8 December 2006 | $10

Science

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Volume 314, Issue 5805

COVER

The grass *Sorghastrum nutans*, one of a dozen plant species that dominate native North American prairies. Biofuels produced from diverse mixtures of prairie plants can provide greater energy yields and environmental benefits than food-based biofuels such as corn ethanol and soybean biodiesel. See page 1598.

Photo: Jason Hill

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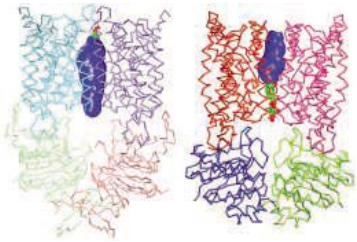

SCIENCE EXPRESS

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Late-Neoproterozoic Deep-Ocean Oxygenation and the Rise of Animal Life
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Secondary siRNAs Result from Unprimed RNA Synthesis and Form a Distinct Class
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A distinct class of small antisense RNAs is synthesized by RNA-directed RNA polymerase from siRNA templates in *Caenorhabditis elegans*.
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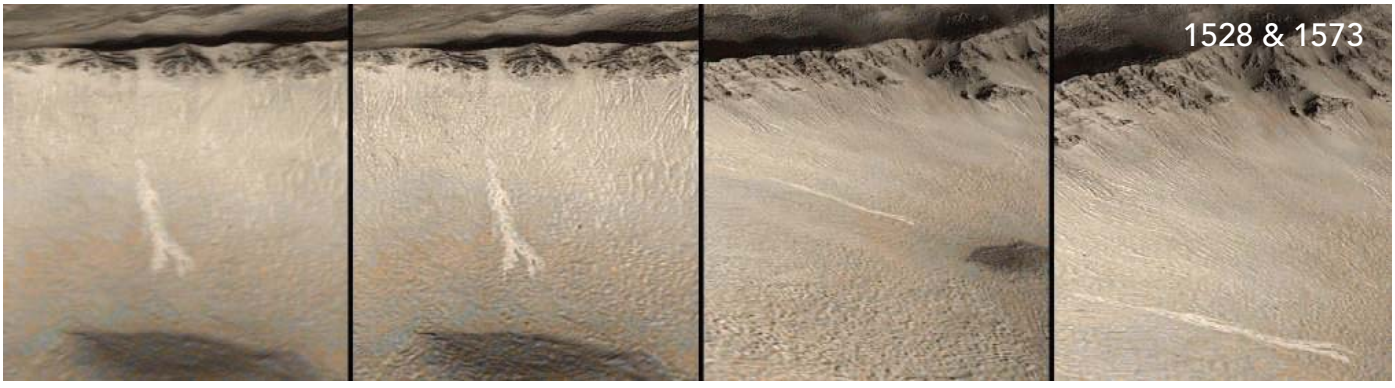

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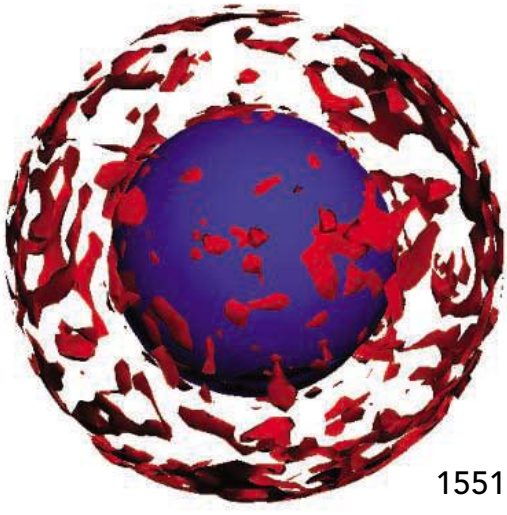

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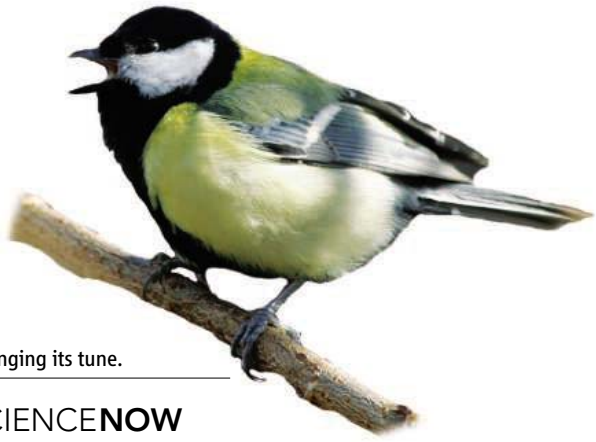

Changing its tune.

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City Bird, Country Bird
Great tits change their tune when they move to the city.

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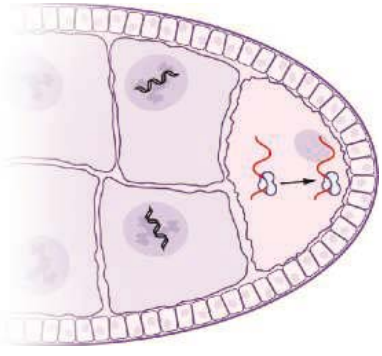
Team models spread of virus to Western Hemisphere.



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SCIENCE'S **STKE**

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PERSPECTIVE: What Is So Special About *Oskar* Wild?
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The function of an mRNA extends beyond encoding protein.

PERSPECTIVE: PI3 Kinases in Cancer—From Oncogene Artifact to Leading Cancer Target
J. J. Zhao and T. M. Roberts
Identifying the roles of different PI3K isoforms may facilitate the use of their inhibitors in cancer therapy.

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With improving budgets, facilities, and leadership, China is becoming a popular destination for young European scientists.

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A. Kotok
Get an overview of China's research system and environment, with tips for China-bound Western scientists.

US/CHINA: Chinese Medicine, Western Style
J. Kling
Western pharmaceutical companies are providing employment opportunities, but mostly for Chinese nationals trained in the West.

US: Opportunities—Intellectual Property, Part 2
P. Fiske
If you think that invention belongs to you, think again.

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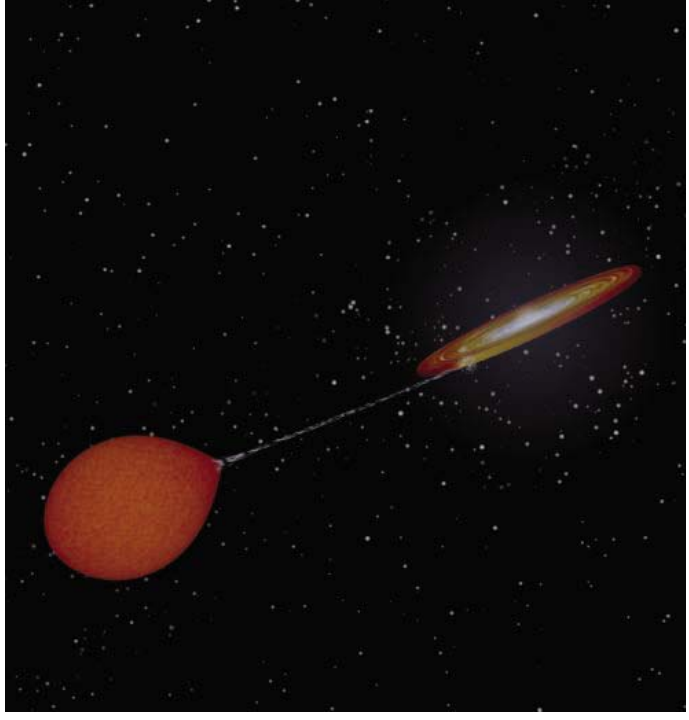
EDITED BY STELLA HURTLEY AND PHIL SZUROMI



Cataclysmic Cannibals >>

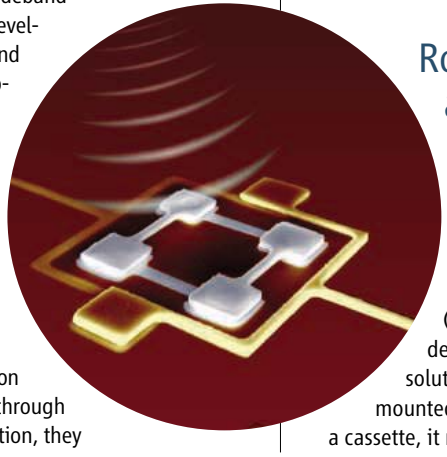
Cataclysmic variables are binary systems in which a compact white dwarf sucks material from its companion star, which causes their light emission to flicker. Theoretical work has suggested that the donor stars in most fast-spinning cataclysmic variable systems should have lost enough hydrogen to become brown dwarfs, but none have been seen. By accurately timing the eclipses in the short-period cataclysmic variable system SDSS 103533.03+055158.4, **Littlefair *et al.*** (p. 1578; see the Perspective by **Maxted**) show that its donor is a 0.05 solar mass brown dwarf, which was likely cannibalized from a normal main-sequence star. The star's mass is slightly greater than its orbital period would suggest, which implies that brown dwarf radii may be underestimated by current evolutionary models.

Mars Changes in Real Time

The thin martian atmosphere does little to protect its surface from bombardment by even small objects from space. **Malin *et al.*** (p. 1573; see the news stories by **Kerr**) have found new impact craters that pockmark the surface of Mars through differencing images from Mars Global Surveyor taken 7 years apart. The impact cratering rate they measured is comparable with that seen for the Moon. Also, they spotted recent changes in the walls of two craters that they interpret as evidence for recent trickles of liquid water.

Cooling on the Side

Devices based on quantum systems generally perform better under cryogenic conditions that minimize thermal noise. However, the lowest temperature achievable is typically limited by the cooling system used. **Valenzuela *et al.*** (p. 1589; see the Perspective by **Chiorescu**) introduce a method of lowering the effective temperature of a qubit by using the sideband cooling technique developed for quantum and atom optics. The two-level system under study, a flux qubit, has an ancillary higher level that is used as a passage level from the qubit's thermally excited state toward its ground state. By driving the population to the ground state through the side-band transition, they can cool the qubit to 3 millikelvin, appreciably lower than the several-hundred-millikelvin temperature of its thermal bath.



Helium to Burn

Stars like the Sun produce ^{3}He as they burn, and when they finally swell to red giants at the end of their lives, the ^{3}He should mix into the convecting outer layers and ultimately be lost in stellar winds. However, very little ^{3}He is seen in interstellar space beyond the predicted amount from Big Bang nucleosynthesis. **Eggleton *et al.*** (p. 1580, published online 26 October; see the Perspective by **Podsiadlowski and Justham**) show by modeling a red giant star in three dimensions that turbulence at the base of the convection zone pushes ^{3}He back down in to the star's engine, where it is burnt further to ^{4}He and H. This turbulence arises from a switch in the mean molecular weight of layers that leads to a Rayleigh-Taylor instability.

Robots, Computers, and DNA

The use of complex DNA pairing and strand-displacement schemes for computing and robotics is the subject of two reports (see the Perspective by **Fontana**). **Ding and Seeman** (p. 1583) have taken a DNA device that normally operates in solution and show that, when mounted on a lattice and placed within a cassette, it retains its functionality. The placement and operation of specific devices at this size scale is a key step in the development of nanorobotics. **Seelig *et al.*** (p. 1585) have designed a set of single-stranded DNA molecules that can be used in a modular fashion to build a series of logic circuits such as AND, OR, and NOT operators, as well as an amplifier and a thresholding device. The devices work by letting an input DNA strand bind to an exposed or unpaired segment of a gate device, which causes a strand displacement.

Later Than Expected for a Date

An important australopithecine, StW 573, has been recovered from Sterkfontein cave, South Africa. Originally, only its foot was recovered, but it now appears that most of the skeleton is available. This hominid has been thought to have lived before 3 million years ago (Ma), and earlier work, based on magnetic stratigraphy and cosmogenic dating, put it as old as 4 Ma. **Walker *et al.*** (p. 1592) dated the cave deposits holding the fossil with the more accurate U-Pb system. Their ages indicate that the fossil formed only about 2.2 Ma, which implies that the South African australopithecines represent hominids living after the development of tools, rather than before.

From Competition to Cooperation

Understanding the evolution of cooperation—whether between genes or cells or within ani-

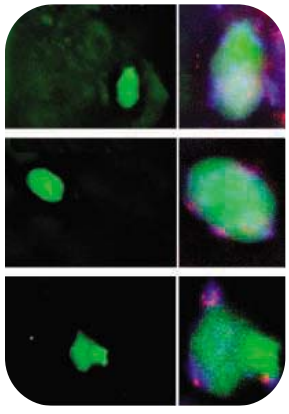
CREDITS (TOP TO BOTTOM): STUART LITTLEFAIR, CHRIS WATSON/SHEFFIELD UNIVERSITY; S. O. VALENZUELA

mal and human societies—remains one of the fundamental challenges of biology (see the Perspective by **Boyd**). **Nowak** (p. 1560) reviews the five main mechanisms of cooperation: kin selection, direct reciprocity, indirect reciprocity, network reciprocity, and group selection. **Bowles** (p. 1569) contends that the ecological challenges facing humans during the late Pleistocene resulted in intense competition for resources, frequent group extinctions, and intergroup violence. Genetic, climatic, archaeological, ethnographic, and experimental data were used to look at human cooperation in an economics-based, cost-benefit model. Members of a group bearing genes for altruistic behavior pay a tax by limiting their reproductive opportunities in order to benefit from sharing food and information, thereby increasing the average fitness of the group, as well as their interrelatedness. Bands of altruistic humans would then act in concert to gain resources from other groups at a time when humans faced daily challenges to survival.

Toward Biofuels

Successful biofuels development will require the creation of microbial strains that have high ethanol and glucose tolerance and necessitate the reprogramming of whole segments of metabolism. **Alper *et al.*** (p. 1565) changed one member of the global transcription machinery so that the levels of the multitude of genes necessary to achieve ethanol and glucose tolerance could be altered simultaneously. To date, biofuels are produced from monocultures grown on fertile soils. These biofuels are ''carbon-positive'' because their production and combustion increases atmospheric CO_2, although not as much as do fossil fuels. **Tilman *et al.*** (p. 1598, see the cover) now find that biofuels produced by polycultures of multiple species can be ''carbon negative'' and may provide a substantial portion of global energy needs in a sustainable and environmentally beneficial manner without competing with food production for fertile lands.

Switching Neurotransmitter Effects in Development



The neurotransmitter GABA generally exerts inhibitory effects on neuronal activity during adulthood, but, during early development when circuits are being built, GABA has excitatory effects. Studying chick neurons, **Liu *et al.*** (p. 1610) show that the change involves a switch in the direction of the chloride gradient across the cell membrane, which is in turn triggered by changes in nicotinic signaling activity. The change in signaling modality may reflect how neuronal activity and cellular development interact to fine-tune the structure of the brain.

From Oscillations to Patterning

During early vertebrate development, blocks of mesodermal tissue, somites, are laid down on either side of the notochord in a periodic fashion following rhythmic waves of gene expression in the presomitic mesoderm. The somites subsequently give rise to skeletal muscle, axial skeleton, and part of the dermis. **Dequéant *et al.*** (p. 1595, published online 9 November) use a systematic analysis of genes expressed in the presomitic mesoderm over time. Oscillations of the fibroblast growth factor and Notch pathways alternated with components of the Wnt pathway, which suggests that an antagonism between these signaling pathways leads to the generation of phased somites.

A Deadly Duo

Human immunodeficiency virus (HIV) and malaria are two of the greatest infectious disease concerns that occur together in tropical regions. The interaction between these pathogens during coinfection is poorly understood, but it seems that infection with one predisposes to infection by the other. **Abu-Raddad *et al.*** (p. 1603) have examined the human population consequences of HIV and malaria parasite coinfection in a high-risk region of Africa. The authors tested their model on data gathered from Kisumu, Kenya, and found that a synergy operates between the pathogens that explains the propagation of many thousands of HIV infections and almost a million malaria episodes since 1980.

CREDIT: LIU *ET AL.*

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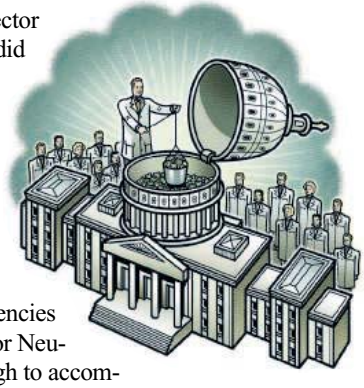
Donald Kennedy is the Editor-in-Chief of *Science*.

Show Us the Money

THE EDITOR'S DESK AT *SCIENCE* IS SO FULL OF COMPLAINTS ABOUT PAPERS THAT IT'S ALMOST a relief when we get something like this, from a department chair at a medical school: "I am wondering why *Science* hasn't been more vocal about the tremendous decline in National Institutes of Health (NIH) funding levels currently being experienced in the United States. This is a true crisis—a tragedy!"

Before calling out the Bengal Lancers, let's review some data. First, *Science* covered the budget allocations for fiscal year (FY) 2007 twice this past summer and published a good Editorial by J. Michael Bishop and Harold Varmus on the issue (*Science*, 28 April 2006, p. 499). Though it's unfair to have called us asleep at the wheel, it is fair to direct our attention to a situation that is producing much anger and frustration. Biomedical scientists are justified in complaining about NIH pay levels, but what about those supported by the National Science Foundation and the Department of Energy?

In analyzing circumstances contributing to the NIH problem in a recent *Science* Policy Forum (*Science*, 17 November 2006, p. 1088), NIH Director Elias Zerhouni pointed out that although the NIH budget doubled, so did the number of grant applications! The current supply/demand problem has other causes too. Institutions that have been churning out new Ph.D.s, assuming that the world would never change, bear some responsibility. Furthermore, the NIH allocation went flat right after it doubled. Annual increases in research costs mean that under constant-dollar funding, NIH loses about a billion dollars a year. NIH management didn't do that—the Congress did for the past 4 years, and all indications are that it will continue to do so.



The problem goes beyond NIH. For example, it and other federal agencies support a lively industry producing tools for research. At the Society for Neuroscience meeting in Atlanta this fall, the exhibit hall looked big enough to accommodate the football game under way at the Georgia Dome. It was full of corporate booths featuring high-tech equipment, symbolizing the interdependence between this growing industrial complex and federal funding. The industry would disappear without that funding: Scientists need the tools, so they order them. Because the real purchaser—the government—cannot control price, the inflation rate for biomedical equipment rises, driving research expenditures upward.

What about the universities? Zerhouni emphasizes that our scientific strength flows from an early, well-understood co-investment between government and academia. We 1960s department chairs welcomed government support for infrastructure to assist faculty growth. As federal budgets tightened, universities used debt or donor financing for new buildings and spent general funds to help new faculty recruits get a head start. Such co-investments enhanced the institution's scope of research and the means to support it, but the trend in federal funding sends a message that Congress and the administration no longer support this historical partnership.

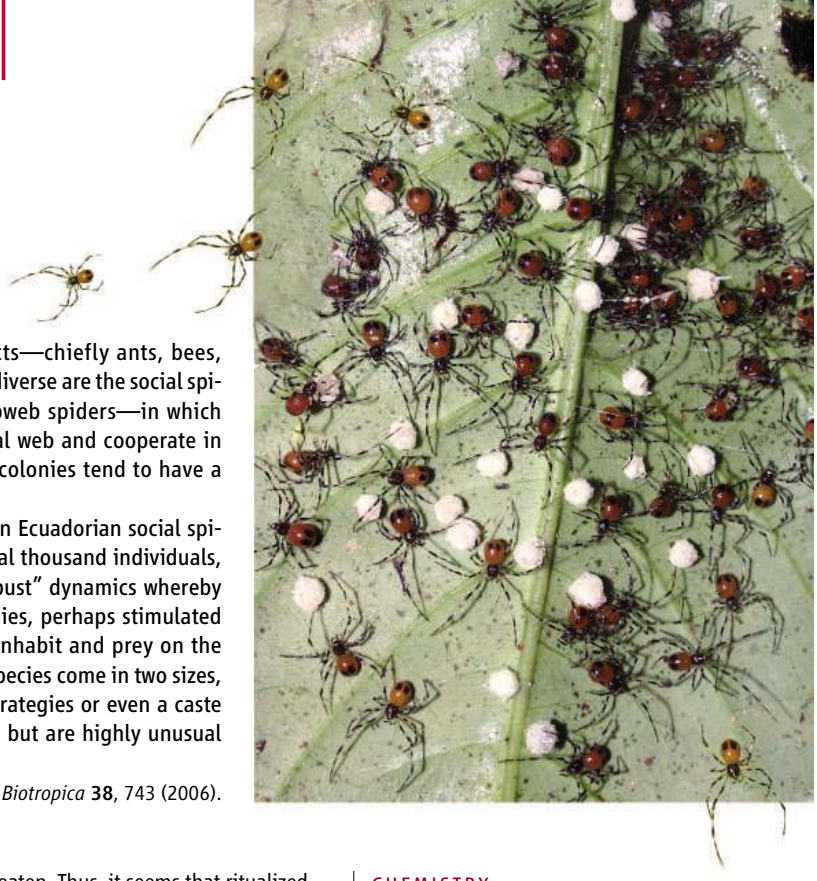
Looking at the research universities amplifies one's unease about the future. New goals for capital campaigns run up to $4 billion, partly to make up for shortfalls in federal funding. Some of the gifts will be for new endowed professorships, whose incumbents will want graduate students and fellows. Some will fund research buildings or programs. The leveraging effect of past government funding has thus prompted larger institutional research commitments. Leveraging by federal funds has thus prompted more institutional commitments. But the current NIH disinvestment will mean trouble for universities, who may be unable to recoup their own recent investments.

Is there a solution? First, scientists might consider advocacy for a research investment floor in all agencies that could keep pace with the growth of research costs, instead of promoting their disciplinary interests at the expense of others. The government must decide whether it wants to preserve the investments made over the past 20 years or instead tolerate long-term damage to our national competitiveness. The biomedical complaints to NIH are misdirected; it's doing the best we can expect. The scientific community has a broader challenge here: to avoid talking about its self-interest and instead tell the administration and Congress and the public what it can accomplish for our society.

– Donald Kennedy

10.1126/science.1137742

CREDIT: PETER HOEY



ECOLOGY/EVOLUTION

A Web of Spiders

Arthropod sociality is largely confined to insects—chiefly ants, bees, wasps, and termites. Less well known and far less diverse are the social spiders—about 20 species, many of which are cobweb spiders—in which large numbers of individuals occupy a communal web and cooperate in the capture of prey. Like social arthropods, the colonies tend to have a highly female-biased sex ratio.

Avilés *et al.* describe the unusual biology of an Ecuadorian social spider. These spiders live in colonies of one to several thousand individuals, proliferating and dispersing with a "boom-and-bust" dynamics whereby large colonies fragment into many smaller colonies, perhaps stimulated by the preference of an associated predator to inhabit and prey on the larger colonies. Intriguingly, the females of this species come in two sizes, which is suggestive of alternative reproductive strategies or even a caste system—possibilities that remain to be explored but are highly unusual outside the social insects. — AMS

Biotropica **38**, 743 (2006).

ANIMAL BEHAVIOR

Submit or Perish

Social animals often pursue a hierarchical lifestyle, whose expression can be observed by third parties in the form of ritualized dominance displays. Primates, for example, use the relatively complex behavior of pseudocopulation between males as a means of affirming and signaling social relationships.

Issa and Edwards show that crayfish not only adopt dominance postures but also exhibit pseudocopulation. Dominance relationships are

***Procambarus clarkii*.**

generally established quickly in pairs of male crayfish, with the dominant individual displaying typical male courtship behavior, including flipping the subordinate onto his back. In more than half of the pairs, the subordinate then adopted a passive supine posture reminiscent of female mating behavior. Pseudocopulating pairs spent less time fighting, with no mortality occurring in the first day. In pairs that did not pseudocopulate, the dominant males were persistently aggressive, and half of the subordinates were killed, dismembered, and eaten. Thus, it seems that ritualized submission serves to increase the chance of survival for the subordinate crayfish, as it does in mammals—an intriguing example of the convergent evolution of social behavior. — GR

Curr. Biol. **16**, 2217 (2006).

IMMUNOLOGY

Losses and Gains

Cytotoxic T lymphocytes (CTLs) monitor the body's cells for damage or infection by detecting changes in fragments of proteins presented on the cell surface by major histocompatibility complex (MHC) molecules. The spectrum of peptides presented depends on cellular machinery that chops the proteins into small pieces, and on endoplasmic reticulum aminopeptidases associated with antigen processing (ERAAP), which lop off N-terminal residues to generate peptides of the correct length for binding to MHC complexes.

Hammer *et al.* show that mice deficient in ERAAP display a large gap in the peptide repertoires presented. However, this hole is filled by a new set of peptides; these peptide-MHC combinations were immunogenic because they stimulated CTL and antibody production by B cells. Nevertheless, the complexes were structurally distinct from those of wild-type cells and appeared unstable because they rapidly disappeared from the cell surface. It will be of interest to investigate the activity of this editing enzyme in situations such as tumor surveillance and viral infection, perhaps with a view to modulating its activity therapeutically. — SJS

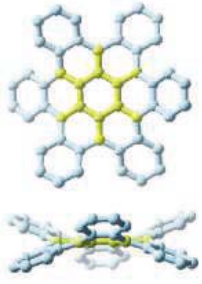
Nat. Immunol. **7**, 10.1038/ni1409 (2006).

CHEMISTRY

Keeping the Charges in Line

Materials that convert sunlight into electrical current not only form electron-hole pairs upon light absorption but also must efficiently transport the carriers to prevent charge trapping and recombination. Disc-shaped liquid crystalline materials such as the contorted hexabenzocoronenes, which naturally form columnar conduit structures, have been studied for use in photovoltaic devices.

Cohen *et al.* find that photoconduction in films of these molecules is exclusively one-dimensional. Optical absorption spectroscopy indicates that the puckered molecular geometry disrupts full delocalization of the π-bonding network. As the molecules stack, the six phenyl rings at the edges interact weakly; only the nearly planar core regions overlap sufficiently for effective π-conjugation. Density functional calculations were used to quantify this observation and indicated a 3.2-eV gap between the highest-energy occupied and lowest-energy unoccupied molecular orbitals in the core, in contrast to a 5.6-eV gap in the outer rings. As a result, these outer rings form an insulating cladding that promotes one-dimensional conduc-



Top and side views of hexabenzocoronene (core, yellow; cladding, blue).

CREDITS (TOP TO BOTTOM): AVILÉS *ET AL.*, *BIOTROPICA* **38**, 743 (2006); ISSA AND EDWARDS, *CURR. BIOL.* **16**, 2217 (2006); COHEN *ET AL.*, *NANO LETT.* **6**, 10.1021/NL0620233 (2006)

tivity in the encircled radialene core. The high charge separation observed in these molecules renders them exciting candidates for applications. — MSL

Nano Lett. **6**, 10.1021/nl0620233 (2006).

CLIMATE SCIENCE

El Niño's Past and Future

The El Niño–Southern Oscillation (ENSO) causes large annual changes in tropical Pacific sea surface temperatures and leads to climate anomalies across the world. Researchers have sought a better understanding of the impact of global warming on ENSO phenomena. However, the limited temporal resolution of the few existing proxies for ENSO events has hindered reconstructions of ENSO variability in the past.

Koutavas *et al.* take an important step toward creating a more detailed paleo-ENSO record by performing oxygen-isotope analyses on single foraminifera and then combining those results with a Holocene sea surface temperature record of the eastern equatorial Pacific. They find that the variability in oxygen-isotope composition of individual forams increased since the mid-Holocene, indicating that ENSO events became more frequent or more intense over that interval. Additionally, opposing temperature variations in the eastern and western Pacific were consistent with a shift in the position of the Intertropical Convergence Zone (ITCZ). Because global warming is expected to shift the ITCZ position even further, there very well could be accompanying changes in ENSO phenomena. — HJS

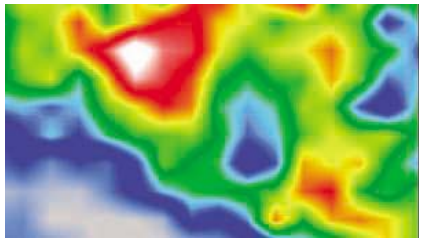
Geology **34**, 993 (2006).

ASTROCHEMISTRY

Anions in Space

Although more than 100 neutral molecules and 14 molecular cations have been identified in space, polyatomic anions have eluded detection. Most detection efforts have focused on small anions for which well-resolved spectra have been measured in the laboratory.

McCarthy *et al*. report rotational spectra for the comparatively large linear triynyl anion C_6H^-. In the millimeter band, absorption spectra were acquired from samples generated by dc discharge of acetylene at low pressures. In the centimeter band, Fourier-transform microwave spectra were



Tracer image of Taurus molecular clouds.

obtained using a molecular-beam source. Spectral shifts for the deuterated isotopomer helped to confirm the assignment. These spectra proved to be an excellent match to a harmonic series observed more than a decade ago in the infrared carbon star IRC +10216 in Leo, as well as to features observed in the Taurus molecular cloud TMC-1. The large size of this anion likely helps it to retain its excess electron despite high fluxes of ionizing ultraviolet radiation in space. — PDS

Astrophys. J. **652**, L141 (2006).

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<< Of Arsenic and NF-κB

Arsenic is carcinogenic at low doses and cytotoxic at higher concentrations. Song *et al*. investigated the mechanisms underlying arsenite cytotoxicity, focusing on nuclear factor κB (NF-κB), which regulates the transcription of target genes when activated by means of IκB kinase (IKK). Although NF-κB generally mediates antiapoptotic signals—in part through inhibiting c-Jun N-terminal kinase (JNK) signaling—under some conditions, NF-κB signaling is proapoptotic. Wild-type mouse fibroblasts were more sensitive to the cytotoxic effects of arsenite than were cells lacking the β subunit of IKK. $IKK\beta^{-/-}$ cells failed to show arsenite-dependent JNK phosphorylation, and inhibiting JNK signaling attenuated arsenite-mediated cell death. Arsenite acted through IKKβ–NF-κB to increase the abundance of growth arrest and DNA damage–inducible (GADD) 45α, whose up-regulation was required for arsenite-induced phosphorylation of JNK. Analysis of fibroblasts from knockout mice implicated the NF-κB1 subunit (p50) in arsenite's cytotoxic effects, and further analysis suggested that GADD45α up-regulation depended on p50-dependent inhibition of ubiquitination and proteasomal degradation. Thus, arsenite-mediated cytotoxicity appears to involve IKKβ–NF-κB-dependent activation of JNK signaling through a mechanism that depends on the accumulation of GADD45α rather than transcriptional activation. — EMA

J. Cell Biol. **175**, 607 (2006).

CREDIT: DAME *ET AL., ASTROPHYS. J.* **547**, 792 (2001)

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Extracting toner in Giuyu.

E-JUNK CRISIS MOUNTS

Delegates from 120 governments met in Nairobi, Kenya, this week to discuss what to do about e-waste, particularly the oceans of electronic junk that arrive daily in poorer countries of Asia and Africa.

According to the United Nations Environment Programme (UNEP), about 50 million tons of e-waste is generated annually—with the United States being by far the largest producer. The Basel Convention, adopted in recent years by most European countries, calls for a ban on the export of all hazardous wastes—which includes electronics because of their toxic components—from rich to poor countries.

But as richer countries try to discourage throwing e-waste in landfills, the "recycling" business has grown apace. About 80% of the world's high-tech rubbish ends up in Asia—90% of that in China, and most of that in Giuyu, north of Hong Kong. After workers extract a few desirable parts, most is left to pollute the environment.

Even goodwill gestures are ending up as junk, according to UNEP Director Achim Steiner. More than half of the computers donated to Africa are obsolete or unusable because of lack of technical support.

There's been some progress at addressing e-waste, however. Last month, for example, three Asian countries signed on to a pilot scheme for the collection and environmentally sound disposal of "end-of-life" mobile phones.

NETWATCH >>

Reef Watching

With reefs under threat from pollution, coral-breaking fishing nets, diseases, climate change, and a host of other causes, keeping an eye on their environment is ever more important. The Coral Health and Monitoring Program from the National Oceanic and Atmospheric Administration provides baseline atmospheric and oceanic data for reefs in the United States and the Caribbean. The site connects to two monitoring networks. One offers hourly readings of air temperature, wind speed, and other variables for eight Florida reefs; the other collects data on additional features such as salinity and light levels at different wavelengths and depths. >> www.coral.noaa.gov

The Last of the Tasmanians

Scientists will be racing to complete a series of studies on the skeletal remains and teeth from 17 aboriginal Tasmanians before London's Natural History Museum turns over the material to the Tasmanian Aboriginal Centre (TAC) next year.

Very few museums have remains from Tasmanian aboriginals, who were driven into extinction by the British. Only a few descendents remain of a dozen women who escaped the slaughter.


1878 photo of Trucannini, the "last" Tasmanian aborigine.

Starting in January, scientists will have 3 months to do studies, including imaging, measurements, and DNA and isotopic analyses, to discern population variation, migration and mating patterns, life spans, pathologies, and dietary habits. The museum's science director, Richard Lane, notes that people of Tasmania, which separated from mainland Australia about 12,000 years ago, were "quite different" from mainland dwellers. For example, he says, unique and varied types of mitochondrial DNA have been found in Tasmanians.

The handover follows many years of negotiations and passage of a new Human Tissue Act that permits British institutions to deaccession such holdings. TAC plans to cremate the remains.

Museum Director Michael Dixon says, "We do not believe that the scientific value should trump all other claims." But Smithsonian Institution anthropologist Douglas Owsley says, "The loss of [remains from] any of these rare groups is very unfortunate." He notes that the planned research will be "no substitute" for techniques that are bound to come along in the next decade or so.

Waltzing on the Lawn

At right is a work by New York City sculptress Mara Haseltine that has been donated to Cold Spring Harbor Laboratory in New York by Human Genome Sciences Inc., the company founded by the artist's father, William Haseltine. Called *Waltz of the Polypeptides*, the 24-meter-long sculpture, based on observations from state-of-the-art cell-imaging techniques, depicts a ribosome in the act of producing an infection-fighting protein.

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EDITED BY YUDHIJIT BHATTACHARJEE

Politics

AN INCONVENIENT DVD. The producer of Al Gore's movie about the threat of global warming, *An Inconvenient Truth*, has picked a fight with the National Science Teachers Association (NSTA) over its refusal to send its members free DVDs of the former vice president's tutorial on climate change. But NSTA isn't backing down.

A 26 November op-ed in *The Washington Post* by environmental activist Laurie David (left)—wife of *Seinfeld* creator Larry David—accused NSTA of kowtowing to one of its corporate sponsors, ExxonMobil. David told *Science* she finds it "shocking" that NSTA would have any ties to a company "that has spent millions misinforming the public about global warming."

NSTA Executive Director Gerald Wheeler says that David's offer of 50,000 DVDs was rejected because of a 2001 policy that prevents NSTA from endorsing any product or message by an outside organization: "We don't do mass distributions for anybody." But Wheeler says he's "not ashamed" of taking money from corporate America—including the oil and gas industry—to help improve science education.

Wheeler says NSTA has offered to mention the movie on its Web site and in its newsletters. David has already rejected another suggestion, to buy NSTA's mailing list, at $130 per 1000 names. "You don't want to send out a cold letter," she says. "There are 1000 reasons why that wouldn't work."

DEATHS

ROLE MODEL. Chinese biochemist Chen-Lu Tsou, who helped synthesize bovine insulin and later campaigned against academic misconduct, died on 23 November in Beijing after a battle with lymphoma. He was 83.

Educated at Cambridge, Tsou led a Chinese team in the 1950s that joined the A and B chains of bovine insulin, which paved the way for the total chemical synthesis of the protein in 1965. He resumed research after the Cultural Revolution ended in the mid-1970s, tackling questions such as how enzymes work.

Tsou also spoke out against academic misconduct in China, most famously, exposing a Chinese-American researcher who gained the trust of political leaders to back his dubious work using messenger RNA to influence goldfish development. Pei Gang, director of the Shanghai Institutes for Biological Sciences, calls Tsou "my role model as an excellent scientist with a high moral standard and social conscience."

MOVERS

BACK TO SCIENCE. William Schlesinger, dean of Duke University's Nicholas School of the Environment and Earth Sciences, will leave in June to become president of the Institute of Ecosystem Studies (IES) in Millbrook, New York. His departure has been driven in part by his unhappiness with Duke's administration.

In his 6 years as dean, Schlesinger boosted fundraising and increased enrollment by 66%. But he recently had disagreements with university administrators over management of the school's policy institute. Schlesinger wanted the institute to report exclusively to him instead of him and the provost. "I was a little frustrated," he admits. Adding to the headaches, a $72 million donation pledged in 2003 by the school's founding donors has not yet materialized.

At IES, Schlesinger, 56, will have a chance to focus on ecosystem science—his specialty. He is taking over from Gene Likens, who founded the institute in 1983.

Three Q's >>

A decadelong work in progress, the National Ecological Observatory Network (NEON) would set up 20 field stations to bring big science to ecologists. Biogeochemist **David Schimel**, who has worked at the National Center for Atmospheric Research in Boulder, Colorado, is taking over as the new chief officer of the project.

Q: What's your vision for NEON?

NEON is going to provide the first integrated view of ecological processes at the continental scale. It will address some fundamental questions in ecology but also some practical questions about how biological invasions and diseases respond to climate and land-use changes.

Q: The project could cost up to $200 million. Is it worth that much?

The pitch is this: Society depends on natural systems in terms of food and fiber. We're vulnerable to wildfire and the spread of infectious diseases. What NEON will do is provide the observational basis for forecasting the effect of ecological processes on the human enterprise.

Q: It sounds like a risky career move for you. Why did you make it?

I'm interested in NEON because it's the culmination of the kind of science I've been working on since I was a graduate student. It will transform ecology, intellectually and logistically. And as a scientist, I've always been fascinated by new ways of looking at the world.

Got a tip for this page? E-mail people@aaas.org

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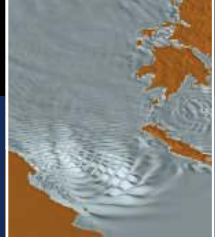


Mediterranean killer
1527

Recent impacts on Mars
1528

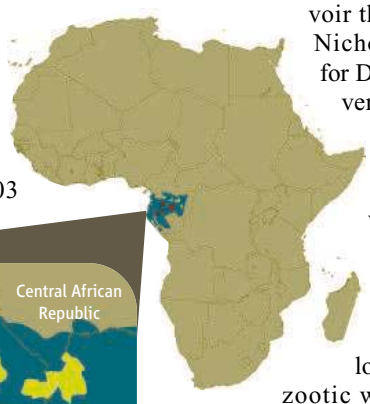
ECOLOGY

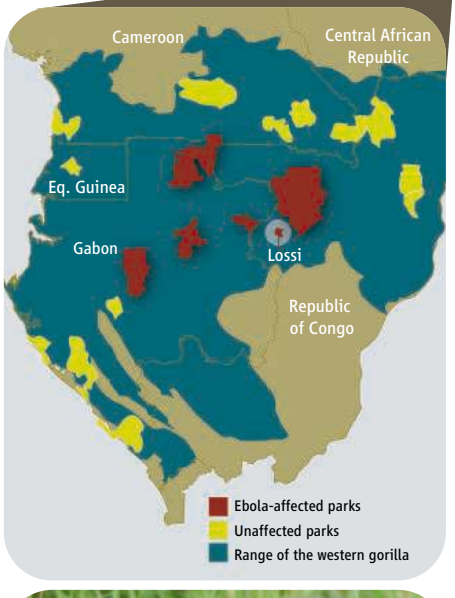
Tracking Ebola's Deadly March Among Wild Apes

It is grim work to document the deaths of nearly all your study subjects. Primatologist Magdalena Bermejo and her colleagues have watched as dozens of the gorillas they had studied either disappeared or turned up dead over the past 4 years. The suspect is Ebola, a hemorrhagic fever that has also killed dozens of people in the region straddling the border between Gabon and the Republic of the Congo. On page 1564, the researchers present evidence that the disease has wiped out as many as 5000 gorillas in the region surrounding the Lossi Sanctuary, a much higher number than previous estimates. They also suggest that ape-to-ape transmission is a major factor in the spread of the disease—which some experts say offers a glimmer of hope for attempts to slow its deadly progress.

As the disease has swept through several wildlife sanctuaries and national parks, killing off chimpanzees and gorillas alike, virologists and great ape specialists have been frustrated in their efforts to explain how the disease is spreading. For years, scientists sharply disagreed on whether apes caught Ebola primarily from a reservoir species, such as bats or birds, that could carry the virus without getting deathly ill, or whether it was mostly spread from an infected ape to its contacts (*Science*, 13 June 2003, p. 1645, and 16 January 2004, p. 298). An answer has proved elusive: Scientists had no idea which of hundreds or even thousands of forest species might serve as a reservoir, and it is extremely difficult to observe whether apes in the wild are passing a virus to each other. But over the last year, a consensus has begun to emerge. Although both mechanisms of spread probably play a role, evidence has been mounting that apes are indeed passing the virus to each other. Bermejo's data support that theory, with some of the best documentation yet of the disease spreading among social groups.

Between October 2002 and January 2003, Bermejo, a primatologist for ECOFAC in Libreville, Gabon, and the University of Barcelona, suffered the disappearance of 130 of the 143 gorillas she and her colleagues had painstakingly habituated for study. Determined to document what was happening, the researchers identified seven other social groups in the area and monitored their sleeping nests twice a week. Between October 2003 and January 2004, they





Deadly spread. In the past decade, Ebola has killed chimps and gorillas across sanctuaries and parks in Gabon and the Republic of the Congo.

report, Ebola killed 91 of the 95 animals. The scientists found that the lag time between deaths in neighboring groups was 11.2 days—similar to the 12-day human incubation period. Combined with a north-to-south pattern of deaths over time, the researchers say, the evidence is very strong that the virus is spreading from one social group to another.

Although he initially favored the reservoir theory, virologist Stuart Nichols of the U.S. Centers for Disease Control and Prevention in Atlanta, Georgia, says the recent evidence has convinced him. Combined with genetic studies of the viral strains that have caused outbreaks over the past 30 years, "it really does look like we have this epizootic wave spreading generally westward through the Congo basin," he says, with ape-to-ape transmission on a local scale.

By extrapolating from more wide-ranging transect surveys they conducted, Bermejo and her colleagues conclude that in a 2700-square-kilometer region surrounding the Lossi Sanctuary, roughly 5000 gorillas have succumbed to the current epidemic. "It is impressive data from a difficult area to work in," Nichols says, but the estimate is not as solid as the group's smaller-scale observations. The researchers tested only 12 carcasses, nine of which tested positive for Ebola. "If this was a human outbreak, you'd want to see a lot more testing" to confirm that a single disease is to blame, he says. Still, he says, "my personal opinion? They're probably right."

Despite the grim numbers, co-author Peter Walsh of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, says he sees hope in the growing consensus about ape-to-ape spread. He has long advocated a vaccination campaign for wild apes. The new data suggest that disease is spreading at a predictable rate, he says, which can help scientists anticipate where it might hit next. At least five candidate human vaccines have been shown to protect monkeys in the lab against Ebola

CREDITS (TOP TO BOTTOM): ADAPTED BY PETER WALSH; THOMAS BREUER, MPI-EVA/WCS

infection, says Walsh, who is pushing to try one in the wild. "There are technical hurdles to jump through. But they're surmountable," he says.

Others are less optimistic. Not only is it difficult to imagine how to reach enough wild apes to slow or stop the spread, says Heinz Feldmann, an Ebola virus vaccine expert at the Public Health Agency of Canada's National Microbiology Laboratory in Winnipeg, Manitoba, but releasing vaccines in the wild might also pose secondary ecological risks. Conservation experts and primatologists "all would like to do something. But no one has a good strategy at the moment," he says.

William Karesh of the Wildlife Conservation Society agrees. He is working with colleagues on preliminary studies to see whether edible bait, such as vaccine-dusted fruit, might be an effective tool. But he says any vaccination campaign is many years away.

–GRETCHEN VOGEL

EUROPEAN RESEARCH

Unprecedented Budget Increase Draws Faint Praise

PARIS—A big research budget going up by about 40% sounds like European scientists have reason to celebrate. But when the European Parliament gave its final seal of approval last week to the Seventh Framework Programme (FP7), a €55 billion, 7-year package to boost science and innovation, the research world seemed less than ecstatic—primarily because many think Europe still doesn't have its priorities right.

Yes, scientists say, they'll get a lot more money—but much less than the European Commission had initially proposed for FP7. Yes, they will get a prize they have long coveted: the European Research Council (ERC), a €7.5 billion scientist-run agency that will reward excellence. But a much bigger chunk—more than €30 billion—will go to the vast, goal-oriented lab coalitions that Brussels loves and most researchers hate.

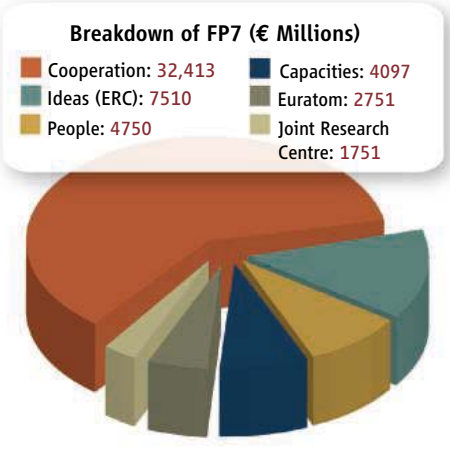
FP7 still needs to be approved by the E.U.'s Council of Ministers later this month, but intense informal talks have assured that it will be. "I feel relieved and tired," Slovenian economist Janez Potočnik, the European commissioner for research, told *Science* last week after the parliamentary vote, which came just in time for the program's formal kickoff in January.

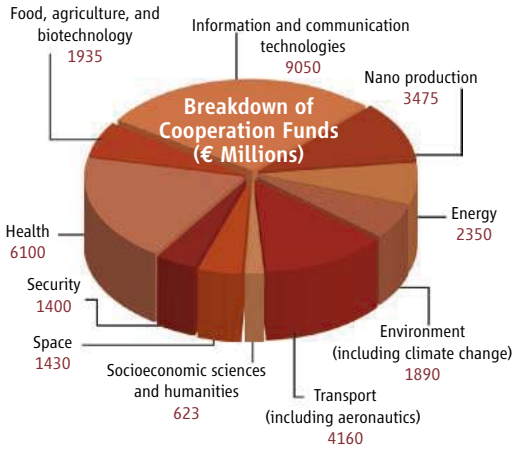
Potočnik had proposed a much bigger shot in the arm for science when he launched the first draft of FP7: some €73 billion over 7 years, which would have roughly doubled the E.U.'s annual contribution to research and innovation. That 2005 plan got stranded in a crisis over the E.U.'s budget (*Science*, 24 June 2005, p. 1848)—a "missed opportunity," given that Europe is still far from its stated goal of spending 3% of gross domestic product on research, Potočnik admits. Still, the 40% increase is "a major change," he says.

The FP7 package, which will run through 2013, has four main pillars. "Cooperation," the E.U.'s pot for applied research projects that require participation from many labs or companies across the continent, gets €32.4 billion. Its three major components address information and communication technologies, health, and transport. "People"—which includes the popular Marie Curie portable grants for young scientists—provides €4.8 billion for training, work abroad, and luring expats back to Europe. "Capacities" contains some €4.1 billion for new research infrastructure, such as radiation sources, data banks, and telescopes. The last category, "Ideas," funds the ERC. Also approved—although technically part of another treaty—is €2.8 billion for Europe's nuclear energy organization, Euratom, most of which will be spent on the International Thermonuclear Experimental Reactor project for fusion research.

Despite its size, the "Cooperation" part leaves many researchers lukewarm. Besides research, it serves lofty goals such as regional development, social equality, and transnational collaboration. The result, researchers say, is a compromise with contracts so burdensome that some researchers don't even bother applying. "You're sending kilos of paperwork to Brussels—it's really a disaster," says Bart De Strooper, a Belgian Alzheimer's disease researcher who led a petition against bureaucracy and in favor of the ERC in 2004.

That kind of criticism is "not fair," Potočnik says. "We have millions of examples of how [Framework] makes people work together across Europe." And although battling the bureaucracy is "a long journey" in Brussels, he promises that FP7 will require less of it. ▶





Big deal. "Cooperation" gets the biggest chunk of research funding; ERC is next, under "Ideas."

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Like researchers, Potočnik seems most excited about the ERC, a new agency akin to the National Science Foundation, at arm's length from politicians. The emphasis on basic science and peer review "is really a terrific development," says Kai Simons, director of the Max Planck Institute for Molecular Cell Biology and Genetics in Dresden, Germany, and chair of the European Life Scientist Organization. He hopes the ERC will help talented young scientists put themselves on the map internationally. "In some countries, it's hard to show that you're good," he says.

Whether Europe has set aside enough money for the ERC is another question. This budget—€7.5 billion for 7 years—is what many consider a bare minimum, says Helga Nowotny, vice-chair of the ERC's scientific council. Indeed, Simons argues that the E.U. should start shifting money from its agricultural subsidies to the ERC at its next budget review in 2009, if only to prevent the success ratio for applicants from becoming so low that "we'll have frustrated people all over Europe." Potočnik doesn't rule it out but says the agency needs to prove itself first. **–MARTIN ENSERINK**

STEM CELL RESEARCH

A Season of Generosity … and Jeremiads

PARIS—One cherished French institution has attacked another in a bruising battle over stem cell research. The Téléthon, France's favorite annual fundraising event, for 20 years has united the country in a massive show of generosity in support of medical research. But this year, Catholic Church leaders have attacked its organizer, the French Association Against Myopathies (AFM), for supporting research that, according to Paris Archbishop André Vingt-Trois, "instrumentalizes the embryo or borders on eugenics." Scientists fear that such harsh words may crimp this year's fundraising and hamper research in areas beyond the immediate target.

Withholding his blessing. André Vingt-Trois, archbishop of Paris, says some work supported by the Téléthon "borders on eugenics."

CREDIT: CHARLES PLATIAU/REUTERS

Thousands of volunteers help raise cash each year for the Téléthon, which grossed a record €104 million in 2005, some 60% of which was spent on research into rare neuromuscular diseases. But since early November, several bishops have taken aim at AFM for supporting work on human embryonic stem cells and genetic studies that have led to prenatal testing and preimplantation diagnosis. "The fact that it's a charity doesn't mean we have to cut it a blank check," Vingt-Trois said in a 27 November radio interview.

AFM says embryonic stem cell research, on which it spent €1.5 million last year, constitutes just one of 440 research projects it supports, and that allowing donors to steer their money to noncontroversial research—Vingt-Trois's personal condition to participate—isn't an option. AFM President Laurence Tiennot-Herment, saying she is "profoundly shocked and saddened" by the accusations, has accused the clerics of abusing the Téléthon to air their viewpoints.

Others have come to the Téléthon's defense. Physician Didier Sicard, who chairs the national bioethics committee, called the Church's intervention "inopportune and extremely uncalled-for" in an interview in *Le Monde*. Evry Bishop Michel Dubost, whose brother died of a muscle disease at age 15, spoke out against his more conservative colleagues in *La Croix*, a Catholic newspaper. And on Monday night, President Jacques Chirac joined the fray in a speech praising the Téléthon as "an exemplary… battle for hope."

Pediatric immunologist Alain Fischer of the Hôpital Necker–Enfants Malades in Paris, although "very upset," says he believes that the flap won't affect the revenues of this year's drive, slated for 8 and 9 December. The people who strictly follow the Church on moral issues "now form a small minority in France," Fischer says. **–MARTIN ENSERINK**

Biotech on the Cape

South Africa has pledged to spend $6 million over the next 4 years to host a new lab in Cape Town sponsored by the International Center for Genetic Engineering and Biotechnology (ICGEB), a U.N. research, training, and technology-sharing agency that now has labs in India and Italy. The new center will initially employ about 25 scientists and staff in five groups starting in May, says Dhesigen Naidoo, who represented South Africa's science ministry last week at a meeting in New Delhi, India, where ICGEB announced this decision. The center's main focus will be the molecular biology of diseases such as HIV/AIDS, tuberculosis, and malaria. South Africa's science minister, Mosibudi Mangena, said he saw it as a step "toward the development of an African biotechnology hub."

–ROBERT KOENIG

Prospecting on the Moon

Space scientists are looking toward a February meeting in Tempe, Arizona, to discuss the lunar base tentatively planned by NASA for 2020 at the south pole of the moon. Instead of several short, Apollo-like missions, NASA wants a four-astronaut outpost that would be fully functioning by 2024. The Shackleton Crater rim offers geologists a chance to explore the 4-billion-year-old Aitken Basin and astronomers an alluring quiet zone for their radio telescopes. **–ANDREW LAWLER**

Growing Minds in the Desert

Saudi Arabia, which spends less on research and education per capita than almost all other countries, announced last week that it will commit $2.6 billion to build the King Abdullah University of Science and Technology in the desert. Undergraduate degrees in diverse fields including biotechnology and computer science will be offered beginning in 2008, with enrollment restricted to Saudis and some foreign "outstanding Muslim students," says a Saudi official. There are no plans yet for a Ph.D. program.

This is the latest step in a recent push for scientific development in the Arab world. But the bottleneck is not money, says Rabi Mohtar, an agricultural engineer at Purdue University in West Lafayette, Indiana, who is working with the Qatar Foundation to boost science in the region. The lack of prestige and opportunities in the sciences drives the vast majority of Arab researchers abroad to study and work. However, "having big educational investments will hopefully raise the level of public awareness," he says, and may entice Arab scientists back home.

–JOHN BOHANNON

NUCLEAR WEAPONS

U.S. Study Finds Slower Breakdown Of Plutonium in Stockpiled Weapons

A new U.S. government analysis has found that the plutonium at the heart of the country's nearly 10,000 stockpiled nuclear weapons is deteriorating much more slowly than expected. The finding, endorsed by outside experts, means that most of the plutonium pits that set off a nuclear explosion could last twice as long as previously thought. That conclusion is likely to escalate the debate over the Bush Administration's campaign to build a new generation of weapons.

The destructive yield of a nuclear weapon can be compromised as bubbles, voids, or even cracks form in its aging pit. Throughout the Cold War, the United States conducted underground blasts to test a bomb's reliability. But in 1993, those tests were replaced by stockpile stewardship, a research program at the nation's three weapons labs that substitutes computers, lab tests, and subcritical explosions.

As recently as May, Department of Energy (DOE) officials estimated that the pits would last from 45 to 60 years. That estimate cast doubts on the future reliability of the W76 warhead, made 30 years ago and carried aboard U.S. submarines. But the new results, delivered in September to DOE headquarters and publicly released last week, suggest that the plutonium in most pits have "credible minimum lifetimes in excess of 100 years." Its conclusion, notes a report from a group of outside scientists known as the Jasons, reduces "near-term concern regarding [the pits'] safety and reliability."

The spherical plutonium pit is at the core of a nuclear weapon, providing the fission reaction that triggers a thermonuclear explosion. Siegfried Hecker, a metallurgist and former director of Los Alamos National Laboratory, calls the material "an engineer's nightmare." Among other problems, uranium, a radiation product, damages the metal's own lattice structure, leaving voids that make the plutonium less compressible and more brittle. Those changes make the pits tougher to implode to achieve critical mass. The new analysis indicates that some fraction of the plutonium atoms resettle back into spots in the lattice, however, helping to preserve the metal's integrity.

In their 7-year study, DOE scientists used a combination of guile and silicon. Researchers scoured stockrooms for applicable plutonium samples and examined the metal's strength, density, and compressibility. New technologies allowed scientists, some of whom hadn't worked on plutonium before, to try different approaches. Putting both decades-old and new samples in the same pressure chamber, for example, "was a first for this program," says Bruce Goodwin, weapons chief at Lawrence Livermore National Laboratory in California. The result was, "the old stuff basically [performed] like the new stuff," he says.

Bubbling up. Decaying plutonium forms internal helium bubbles (*right*) that eventually degrade aging weapons such as the W76 warhead atop this Trident II missile.

To find out how aging would affect even older samples, researchers doped plutonium samples with faster-decaying isotopes to speed up the aging process, incubated the samples in climate-controlled cells alongside newer plutonium, and measured swelling. The researchers then used the 100-teraflops IBM Blue Gene machine at Livermore—the crown jewel of DOE's formidable supercomputing effort—to model the aging process. "The machine was predicting a very slow rate of aging," says Goodwin. Scientists validated that result, they say, with the laboratory data collected from old, new, and artificially aged plutonium. Raymond Jeanloz, a University of California, Berkeley, planetary geophysicist and Jason member, calls the result heartening and indicative of the "wonderful job" the labs have done on stockpile stewardship.

But Hecker, now at Stanford University in Palo Alto, California, says the labs are giving the thumbs-up too soon. He would like to see data from experiments simulating conditions that the older pits would face if the weapons were fired, including high *g*-forces or temperature extremes. Others question whether the simulations build on data from enough actual blasts.

Just what the latest results will mean for the future of the stockpile is up for debate. "Sooner or later, the effects of plutonium aging will require all our current pits to be remanufactured," National Nuclear Security Administration chief Linton Brooks told Congress last year. New pits will still be needed for new weapons, he and other officials argue, because the computer-dependent answers from the stockpile stewardship program will become less reliable as time passes. For those reasons, the Bush Administration wants to build a new pit factory and a new weapon—called the Reliable Replacement Warhead (RRW)—that would use less nasty chemicals and be difficult to detonate if stolen by terrorists. A multiagency panel reviewing early designs of the proposed weapons said last week that plans for the new weapon should progress despite the plutonium findings.

But those plans are controversial. An aide to Representative David Hobson (R–OH), outgoing chair of the House panel that funds the nuclear weapons complex, says that DOE officials have used the shelf life of plutonium as a key measure of the arsenal's health. "That chain of logic makes plutonium aging central to the RRW rationale," says the aide, who says the new data undermine the RRW argument.

The new analysis "buys us time to do the right thing for RRW," says physicist Roy Schwitters, chair of the Jason steering committee. Next month, the group begins a review of RRW itself. **–ELI KINTISCH**

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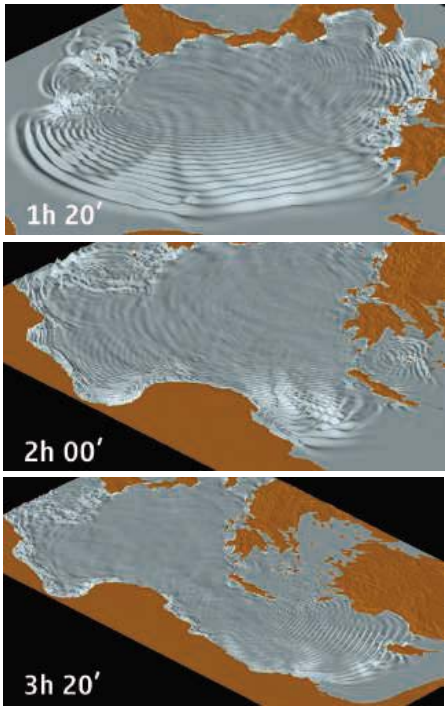
GEOPHYSICS

Ancient Cataclysm Marred the Med

It's a terrifying vision: A violent eruption of Italy's Mount Etna triggers a massive collapse of one flank of the volcano, sending 35 cubic kilometers of debris—the equivalent of 10,000 Cheops pyramids—hurtling at 400 kilometers an hour into the Ionian Sea. The Big Splash unleashes a 50-meter-tall wall of water that, within a few hours, wipes out coastal settlements across the Mediterranean. This catastrophe happened 8000 years ago—and a Mediterranean monster of similar magnitude could happen again.

That's the scenario invoked in an analysis in last week's *Geophysical Research Letters*. "It was an extraordinary event, probably the largest tsunami unleashed in the Mediterranean in the past several millennia," says co-author Maria Pareschi of the National Institute of Geology and Volcanology (INGV) in Italy, whose team announced its findings at a press briefing in Rome on 5 December.



Ripple effect. An Etna collapse 8000 years ago spawned a huge tsunami.

CREDIT: M. T. PARESCHI *ET AL.*, *GEOPHYSICAL RESEARCH LETTERS* (2006)

The paper may solve a long-standing puzzle about the cause of an ancient, devastating tsunami known from sea-floor sediments. "This is a very careful and reasonable work," says Stéphan Grilli, an ocean engineer at the University of Rhode Island, Narragansett. Not everyone agrees. The INGV model has fatal flaws, argues Costas Synolakis, a top tsunami modeler at the University of Southern California in Los Angeles. "The lost tsunami is yet to be discovered," he says.

The Mediterranean basin is a crucible of killer waves. More than 300 tsunamis have been recorded in the last 3300 years, with volcanic activity known to have triggered a dozen in the last 2 millennia. The most recent occurred in December 2002, when a colossal chunk of the Stromboli volcano slid into the Aeolian Sea, creating a 10-meter-high tsunami that snapped moorings of oil tankers in Milazzo harbor 100 kilometers away but did little other damage.

That was a kiddy wave compared to one that left a trail of sediment between Sicily and North Africa. The leading suspect has been a collapse of the Santorini volcano in the Aegean Sea some 3600 years ago. However, INGV's simulations suggest that the Santorini event was largely confined to the Aegean.

The INGV researchers fingered Etna, a highly active volcano on Sicily, as a likely culprit. They carried out seismic surveys and found telltale debris from a landslide spreading 20 kilometers off Sicily. The team carbon-dated the debris to about 8000 years ago. Next, they mapped similarly aged mudslides that flowed hundreds of kilometers, from the Ionian Sea all the way to the Sidra Gulf off Libya. Corroborating evidence comes from an excavation at Atlit-Yam, a coastal village in present-day Israel, which appears to have been abandoned suddenly 8 millennia ago.

Synolakis is unconvinced. He says INGV's model uses "unrealistic" initial conditions, including an impossibly fast underwater velocity of the Etna collapse. Pareschi counters: "Even taking the slowest speed that we considered, the tsunami would occur."

Not in dispute is the notion that volcanism could spawn future megatsunamis. Sicily, Stromboli, and other volcanic islands should be monitored closely, says Grilli. But the worst nightmare may be spawned farther afield. Last year, scientists warned that a massive collapse of Cumbre Vieja, a volcano in the Canary Islands, would trigger a towering tsunami that could pummel coasts on both sides of the Atlantic. Such a collapse could be 10 times larger than the Etna slide—an "immense geological event," says Pareschi. Forget Atlit-Yam: Such a doomsday wave could overwhelm settlements with familiar names, like New York, Miami, and Lisbon. **–JACOPO PASOTTI**

Jacopo Pasotti is a writer in Basel, Switzerland.

My, How That Sun Shines

The dealmaking continues for both the Scripps Research Institute and the state of Florida. Last week, Scripps officials announced a $100 million pact with Pfizer that grants the world's largest drugmaker access to 47% of the institute's discoveries for the next 5 years. The agreement succeeds a similar deal with the Swiss pharma giant Novartis that expires at the end of this year. According to Scripps spokesperson Keith McKeown, the difference between the deals is that Pfizer scientists will have an opportunity to take a more hands-on role in ongoing research. But McKeown says, "we still have complete control over the direction of our research."

The deal could be a boon for Florida, which paid $310 million to lure the California research giant to open a branch in Palm Beach County. According to the terms of that deal, Scripps must pay Florida 15% of the royalties it earns on technology developed in the state, up to $155 million. Meanwhile, Florida's pharma connections may also be growing. This week, Scripps's Florida outpost and two south Florida universities are hosting a delegation of 25 Swiss scientists, business executives, and government officials looking to expand their collaborations with bioscientists in the Sunshine State.

–ROBERT F. SERVICE

Progress for Bioethics Rules

SEOUL—Hoping to close loopholes exploited during the Woo Suk Hwang cloning scandal, South Korea's National Bioethics Committee has approved stronger regulations on sperm and egg donations for research and medical use. The committee is still mulling a proposal to ban researchers from transplanting human stem cells into nuclei-removed embryos of humans or other primates.

Scientists say that nuclear transfer could lead to insights into cures for spinal cord injury or diseases such as Parkinson's. Activists fear that such research could allow researchers to create chimeras. Less-contentious provisions include prohibiting minors or women who have never given birth from donating eggs. Also banned are donations in which coercion between donor and recipient is possible—such as a junior researcher donating for an experiment, as had occurred in Hwang's lab. Although barred from selling eggs, donors can be compensated for their expenses. After the committee decides whether to propose a nuclear-transfer ban, the rules would require approval from the National Assembly before they become law. **–D. YVETTE WOHN**

PLANETARY SCIENCE

Mars Orbiter's Swan Song: The Red Planet Is A-Changin'

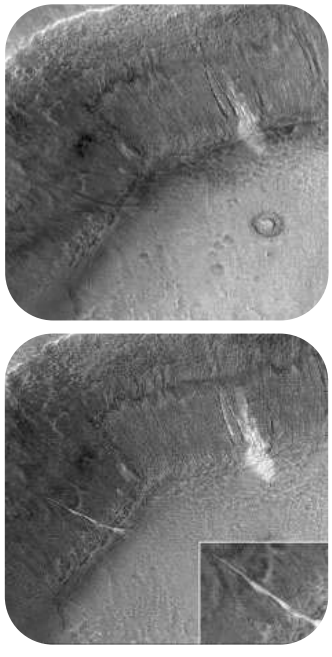
A late hit. Twenty meteorites a few meters across, such as this one, appear to have peppered part of Mars in the past 7 years.

The Mars Global Surveyor (MGS) spacecraft had a great run, but after 10 years and more data returned than all earlier missions combined, it has passed on. NASA lost contact with the orbiter last month and has no new tricks up its sleeve for getting it back. But as the MGS family begins to mourn its loss, members of the camera team are making a twofold tribute. Thanks to MGS's longevity, its Mars Orbital Camera (MOC) was able to keep an eye on large areas of Mars over many years. Dust blew from here to there, but substantial geological change seemed so slow as to be undetectable.

Now MOC has caught the face of Mars aging just a bit—and doing so in remarkable ways. On page 1573, MOC team leader Michael Malin and colleagues at Malin Space Science Systems (MSSS) in San Diego, California, report that water appears to have flowed down two gullies sometime during the past few years, even though liquid water can't long persist on the cold, nearly airless martian surface. "This is the sort of thing you dream about, what everybody's been waiting for," says planetary scientist Jennifer Heldmann of NASA's Ames Research Center in Mountain View, California. The discovery lends support to the existence of liquid water so near the surface, at least in places, that it can spurt out on rare occasions. And where there's liquid water, there could be life.

MOC also found signs of more violent geological change: 20 high-velocity impacts that seem to have struck in the past few years. That could provide a way to calibrate the crater-counting "clock" geologists use to date geologic events on Mars. "If Malin *et al.* are right, then we can get dates for small martian landforms," such as glaciers and young lava flows, says planetary scientist William Hartmann of the Planetary Science Institute in Tucson, Arizona. "That would be wonderful."

Malin and the MOC team have long been hunting for modern gully flows. They were the ones who in 2000 first reported ravinelike features cut by some fluid—presumably water—in the slopes of cliffs and crater walls. The tens of thousands of gullies now known often look so fresh that they might have formed in recent years, but it could have been millions of years ago.



Martian weeping. New deposit (*bottom*, *left*) formed since top image was taken may be water-borne debris.

So since 2000, MOC has reimaged thousands of gullies, looking for any change. In two preexisting gullies, it found, a lighter-toned material had flowed down both widely separated gullies between one imaging and the next. Judging by the way the material flowed around obstacles and splayed into numerous branches, the fluid debris was charged with liquid, they say—most likely water.

Liquid water has been a hot topic in planetary science of late, so signs of it on Mars—on the surface, no less—are generating cautious excitement. "It's fascinating," says Heldmann. "There's clearly something that happened." It doesn't appear to have been any of the nonwater alternatives, such as dry dust avalanches; the most plausible explanation would be water-soaked debris briefly gushing down a gully, she says. "The discovery is the first physical evidence that liquid water exists on Mars today," says planetary scientist Martha Gilmore of Wesleyan University in Middletown, Connecticut. Given the absence of snowbanks or even frost, the water appears to have come from beneath the surface, perhaps from an outcropping aquifer normally sealed by ice.

"Maybe these things are popping off today," says planetary geologist James Rice of Arizona State University in Tempe. "That would be amazing, but I'm not convinced we're seeing modern fluid flow. That would be a big deal. Best err on the side of caution."

Researchers are greeting the MSSS group's report of modern meteorite impacts with a similar mix of excitement and caution. Quite by chance, MOC imaged an area that showed a dark, kilometer-wide splotch that wasn't there before. Taking a closer look, MOC revealed a fresh-looking impact site of seven clustered craters in the middle of the dark spot, which turned out to be dark impact ejecta and dark surface rock that was revealed when the impact blew bright dust off the surface. After this discovery in January 2006, MOC resurveyed 21.5 million square kilometers of Mars that had last been imaged in 1999. The survey turned up 20 impacts during the 7 years, ranging in crater diameter from 2 meters to 148 meters.

That's a surprisingly heavy barrage of impactors—surprising to some, at least. Crater formation is the ticking of the clock that planetary scientists use to gauge how old a surface is: The fewer

CREDITS (TOP TO BOTTOM): MSSS/JPL/NASA; MALIN *ET AL.*

craters, the younger the surface. To find an age for small, relatively young features like glaciers and gullies, researchers must use the more abundant small craters. But they haven't been able to agree on where most small impactors come from (*Science*, 26 May, p. 1132). Do they fall in a steady drizzle from the asteroid belt, like sand through an hourglass? That would be helpful for dating, and the MOC discoveries roughly fit the latest estimate of the rate of such a steady drizzle. Or do they mostly come in bursts when really big impacts splatter the planet with bits of debris once in a million years or so? That could be bad for dating, but if so, MOC shouldn't have seen any new craters.

The MOC result "is a calibration of the actual impact rate at Mars," says cratering specialist Clark Chapman of Southwest Research Institute in Boulder, Colorado. "That's an amazing and excellent result." But it isn't likely to settle the debate right away. Chapman notes that these new craters are smaller than the ones a few hundred meters across used in most dating. And planetary geologist Alfred McEwen of the University of Arizona in Tucson has his doubts about the modernity of the small craters. They may be older craters, he says, just now revealed by the wind blowing bright dust away.

Both active gullies and new craters cry out for scientists' perennial wish: more data. As luck would have it, MOC's successor—the far more capable High Resolution Imaging Science Experiment (HiRISE) camera aboard Mars Reconnaissance Orbiter—started routine operations just last month. So McEwen, principal investigator of HiRISE, is targeting both new craters and active gullies in the coming weeks. MOC's observations "are definitely important," he says, "so let's take a closer look at them." **–RICHARD A. KERR**

GEOCHEMISTRY

A Shot of Oxygen to Unleash the Evolution of Animals

All animals need oxygen, but they haven't always had enough of it to reach their full potential. Earth developed a trace of oxygen—at least in the atmosphere—more than 2 billion years ago. That was just before the appearance of sophisticated cells called eukaryotes in the fossil record. Eukaryotes went on to give rise to animals, but not until about 575 million years ago. Why the wait? For half a century, paleontologists have speculated that only then did oxygen levels rise high enough to support large, active creatures. The evidence for such a jump in oxygen, however, has been sparse and indirect.

Now the theory's proponents can breathe easier. In two papers published this week, researchers present geochemical and isotopic evidence that substantial amounts of oxygen first reached the deep sea 580 million years ago. In one place, the gas seems to have arrived there just 5 million years before macroscopic animals make their debut in the fossil record.

"I'm really thrilled to see this," says geochemist Timothy Lyons of the University of California, Riverside. "I see two really different approaches looking at very different sections [of rock] coming up with similar conclusions. Whether it's a slam dunk, time will tell."

There's still no single, thoroughly unambiguous "paleobarometer" for ancient oxygen, says geochemist Louis Derry of Cornell University. An odd shift in the mix of sulfur isotopes marked the first appearance of even a trace of oxygen 2.4 billion years ago (*Science*, 17 June 2005, p. 1730). And the isotopes of trace metals such as molybdenum have been used to infer that the little oxygen in the atmosphere between 2.4 billion and 0.58 billion years ago had not penetrated below surface ocean waters.

To tease out the history of oxygen around the time of the first animals, two groups applied different paleobarometers to rocks from opposite sides of the world. Geochemist Donald Canfield of the University of Southern Denmark in Odense and colleagues report online in *Science* this week (www.sciencemag.org/cgi/content/abstract/1135013) how they analyzed the iron in a sequence of marine rock in Newfoundland, Canada. They separated the iron into two groups: iron minerals that had been geochemically and biologically active, and iron that was inert. They compared the proportions of each group with the proportions in modern and well-understood older environments. The results showed that the deep sea was probably oxygen-free during the Gaskiers glaciation of 580 million years ago—the last and least of three great, possibly globe-enshrouding glaciations late in the Proterozoic Eon.

Heavy breathers. Enigmatic frondlike animals of the Ediacaran fauna appeared soon after deep-sea oxygen levels rose high enough to support them.

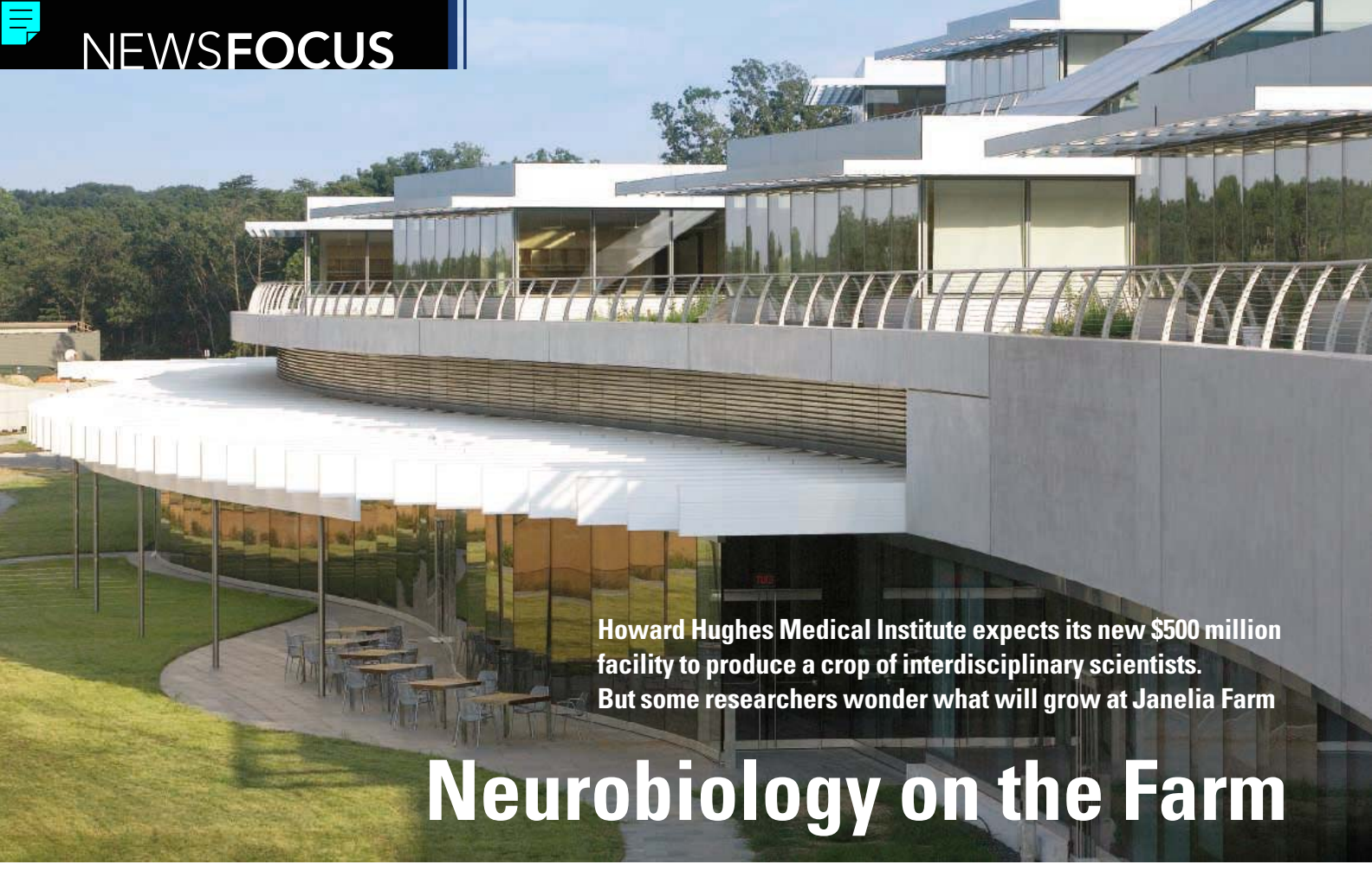
CREDIT: G. NARBONNE

But at the end of the Gaskiers glaciation, deep-sea oxygen appeared, reaching levels that would have required an atmospheric abundance roughly 15% of today's. That's about how much oxygen the first large animals—the odd disks, fronds, and spindles of the Ediacaran fauna—would have needed once they evolved from their presumably near-microscopic, wormy ancestors. And in Newfoundland, the first Ediacara appear 5 million years after the Gaskiers and the rise in oxygen.

On the other side of the globe, in Oman on the Arabian Peninsula, geochemist David Fike of the Massachusetts Institute of Technology in Cambridge and colleagues have found a similar step-up in oxygen recorded in marine rocks drilled by Petroleum Development Oman. This week in *Nature*, they report on three apparent oxygenation steps. They deduce the steps from the way pairs of carbon and sulfur isotopes change as the rocks become younger up the drill hole. The second oxygenation step, around the end of the Gaskiers glaciation, was by far the largest.

The two papers are being greeted warmly, although inevitably with caution. "Especially with these old rocks, you never have enough information," Derry notes. Even so, "the two papers are suggesting similar results from different techniques from different places," he says. "Coming together, they suggest there's a real story here."

Paleontologist Andrew Knoll of Harvard University agrees. The papers "advance the argument that Earth and life are closely related through time," he says. The cause of higher oxygen levels remains unclear. It may go back to the invasion of land by rock-weathering fungi and lichens, or a burst of mountain building. Cracking that one will take a lot more information. **–RICHARD A. KERR**



Howard Hughes Medical Institute expects its new $500 million facility to produce a crop of interdisciplinary scientists. But some researchers wonder what will grow at Janelia Farm

Neurobiology on the Farm

SEAN EDDY WAS LIVING WHAT MANY would call a researcher's dream. A computational biologist specializing in the search for RNA genes, Eddy was not just a tenured professor at Washington University in St. Louis, Missouri, but also a Howard Hughes Medical Institute (HHMI) investigator. But between teaching, advising students, and supervising his lab, Eddy felt the scientific zest fading from his life. "I was in too much of a leadership role and too little of a scientific role," he says.

That restlessness made him an easy target for HHMI Vice President Gerald Rubin, who was in the market for some two dozen group leaders to fulfill the nonprofit's dream of creating a campus devoted to interdisciplinary biomedical research. After hearing Rubin give a talk at a meeting of HHMI investigators at the institute's headquarters in Chevy Chase, Maryland, Eddy didn't hesitate. He walked up to Rubin and said: "Sign me up. This is exactly how I want to do my science."

Now Eddy, at 41, has that chance. In August, he gave up the university life and moved to Janelia Farm, a sprawling 400-hectare research park about 65 kilometers west of Washington, D.C., in Ashburn, Virginia. His new six-person lab, located in a gleaming three-story edifice built into a green hillside, is about half the size of his previous setup. He's free of the administrative responsibilities that took up to a quarter of his time, and he doesn't have to teach courses or apply for research grants. Even more important, he says, is the chance to apply his expertise in RNA genes to neurobiology—an area that has intrigued him since his postdoc more than a decade ago.

Handpicked. Gerry Rubin has recruited scientists with a hunger for interdisciplinary research.

"In academia, at this stage of my career, I am expected to be an empire-builder. But I was looking for an environment where I could work with my own hands and talk to colleagues about ideas and experiments, not grants and FTEs [full-time equivalent positions]," he says. "Now I have almost as much time to do science as I did when I was a postdoc. I have time to read the literature again. It's heaven."

Not everyone sees HHMI's grand experiment in such a favorable light. Academic researchers—including many HHMI investigators—are watching with a mix of envy and skepticism. HHMI has spent $500 million to build Janelia, which will cost $100 million a year to run once it reaches its capacity of 250 researchers by 2009. That investment is an imprudent gamble, say some scientists, adding that biomedical research would have been better served if HHMI had spent the money to expand the network of 302 university-based investigators it now supports.

Critics also say that Janelia's predefined focus on neurobiology violates the spirit of open-ended research that drove the two labs

CREDITS (TOP TO BOTTOM): PAUL FETTERS; ELENA DORFMAN

Open science. Rafael Viñoly's sweeping glass building follows the contours of the land.

it is seeking to emulate: the Laboratory for Molecular Biology (LMB) in Cambridge, U.K., and AT&T's Bell Labs in Murray Hill, New Jersey. And some are turned off by the implicit claim that Janelia will provide a better environment for long-range, interdisciplinary science than is found in academia. "To say that the way science is currently done in America is not effective, that having scientists write grants and teach students is counterproductive—that's just pure arrogance," says Richard Morimoto, a biochemist at Northwestern University in Evanston, Illinois. "Unless these guys produce some extraordinary accomplishments, they'll be ridden out of town on a rail."

Food for thought

Eddy and his colleagues at Janelia—which officially opened in October with more than half of its group leader slots still to be filled—are being asked to create a new model for doing science. Janelia's scientific mission is to understand how neural circuits drive behavior in simple organisms: An example would be unraveling the molecular events in a fly's brain as it zeroes in on a grain of sugar. To accomplish that goal, Janelia scientists expect to develop new imaging technologies as well as novel genetic and computational approaches.

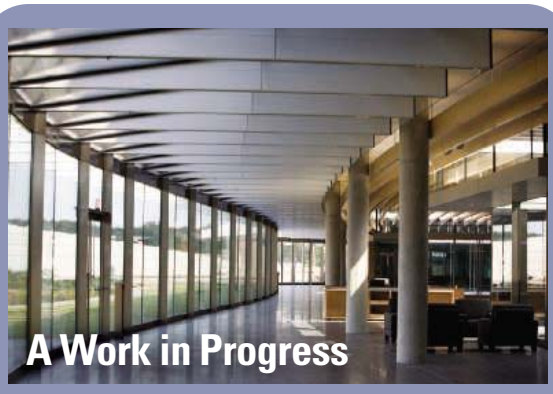
But Rubin is hoping for even more. His premise is that planting talented scientists from different disciplines under one roof and nourishing them with internal funding will result in a rich harvest of fundamental breakthroughs that wouldn't have been possible otherwise. Rubin wants Janelia to attain the kind of glory that LMB earned with discoveries such as the structure of DNA and Bell Labs earned with innovations such as the laser. "We want our researchers to work on problems that are so hard that they don't know if they will be able to solve them," says Rubin, an acclaimed *Drosophila* geneticist who spent his doctoral years at LMB before working as a professor at Harvard University, the Carnegie Institution, and the University of California, Berkeley, and then coming to Hughes in 2000. "Nobody should expect any payoffs for at least 10 to 20 years."

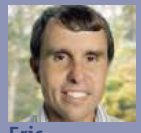
A visitor's first glimpse of Janelia is an open field on the edge of a hill. But drive around the hill, beyond the security checkpoint, and the park's main building comes into view. Designed by award-winning architect Rafael Viñoly, the structure is shaped like an arc about 275 meters long, with floors that jut out of the hillside like steps. The walls are made of glass, giving the building the appearance of a giant fishbowl.

The interior is designed to maximize interactions between researchers, with food as an essential element. A subsidized cafeteria is open from 11:30 a.m. to 1 p.m., an intentionally short window in order to increase the odds that scientists will run into each other during lunch. There's also a state-of-the-art gym and a well-appointed pub featuring billiards and table tennis as well as a bar counter made of exquisite Moroccan fossil stone. After-hours socializing is fueled by discount-priced dinners for staff members and their families: "We serve the best steak you can get for $3.50," boasts Rubin.

Janelia's promise of collaborative science has drawn a mix of early and midcareer researchers. Four of the 10 group leaders hired so far are recent postdocs, and three are university professors, including one whose Louisiana State University lab was destroyed last year by Hurricane Katrina. Two come from the faculty of Cold Spring Harbor Laboratory (CSHL) in New York, where Rubin spent two summers as an undergraduate. One group leader is a former Bell Labs researcher who was working independently at home when he got Rubin's call. All are on 6-year contracts, which can be renewed; if they leave, they have the option of becoming HHMI investigators.

By training, two of the group leaders are computational biologists with no experience in neurobiology, and one is a physicist; the rest are physiologists, cell biologists, biochemists, and neuroscientists with track records in neurobiology. Six of the group leaders have had some research experience at LMB or Bell Labs, and they say those postings shaped their decision to move to Janelia. Two, Eddy and neurobiologist Karel Svoboda, formerly of CSHL, were also Hughes investigators. (Janelia has also appointed six scientists to run one- or two-person labs for 5 years; the goal is to have 20 such fellowship positions.)

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Dmitri Chklovskii


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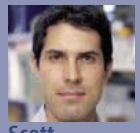
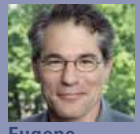

Scott Sternson


Alla Karpova


Loren Looger


Jeffrey Magee


Eugene Myers


Julie Simpson


Karel Svoboda

Team players. Ten of 24 group leader positions have been filled; stovepipe scientists need not apply.

Some of the researchers are self-admitted academic misfits. Eric Betzig, for example, a physicist who developed microscopes at Bell Labs before joining his family's machine tools business in the mid-1990s, says he avoided academia because "at universities, they teach you to do hands-on research only to turn you into an administrator." Computer scientist Eugene Myers, who developed key algorithms for assembling the human genome sequence while at Celera Genomics and in 2002 became a professor at the University of California, Berkeley, says he was disillusioned with disciplinary silos in academia. Janelia's research culture, he says, is "a singularity."

Rubin has imposed workplace rules designed to promote the culture of hands-on, interdisciplinary science. He hopes limiting groups to six people will enhance collaboration. Scientists are required to spend 75% of their time on campus, and they are expected to choose their meetings carefully. "I've heard all the standard objections to these rules from the community, that science is too complicated nowadays to be done by small groups and that people need to travel all over the world to go to meetings," says Rubin. "I don't think that's true."

CREDITS (TOP ROW): PAUL FETTERS; (2ND ROW) PAUL FETTERS (3); MATTHEW SEPTIMUS; (3RD ROW) SUSAN DOOLEY; BARBARA RIES; TOM KLEINDINST; PAUL FETTERS; (4TH ROW) PAUL FETTERS (2)

Group leaders say they are eager to pursue projects that might be deemed too risky for funding by the National Institutes of Health (NIH), including Janelia's goal of developing imaging tools and linking neural circuits to specific behaviors such as feeding. Dmitri Chklovskii, for example, a neuroscientist who's moving to Janelia from CSHL, intends to collaborate with computational biologists and imaging experts to automate a three-dimensional rendering of the fly brain. "There's so much skepticism in the community about whether that can be done that I wouldn't waste any time asking NIH to fund it," Chklovskii says.

Scott Sternson, finishing up a postdoc at Rockefeller University in New York City, is planning an array of experiments to pinpoint the behavioral output of neural circuits in the hypothalamus, a poorly understood structure of the brain. Rather than gathering a lot of preliminary data on a specific behavior, Sternson plans to "take a wider view" and look at multiple behaviors, for which he will need to develop new tools and tests. "By trusting my judgment," he says, "Janelia is allowing me to take a scientific risk." Rubin's plan to spark new ideas by bringing different disciplines together also seems to be working. Geneticist-turned-neuroscientist Julie Simpson, a group leader who is imaging the fly brain, says lunchtime discussions with Betzig and other optical experts are helping her to refine experimental techniques and get higher resolution pictures. "We are also discussing how to automate some of the dissection and staining procedures to speed up prep time for more brains," she says.

Thirst for knowledge. Researchers are encouraged to socialize and dine at Janelia's elegant in-house pub.

Risky business

Although outsiders praise the talent level of Janelia's initial pool of researchers, some question whether those scientists will be able to accomplish anything more remarkable than what they might have achieved elsewhere. Skeptics also wonder whether Janelia's remote location will make it harder to create a vibrant intellectual atmosphere. "It will be a relatively small enterprise compared to Bell Labs, and it will not have LMB's advantage of being situated within a major research university [Cambridge]," says William Newsome, an HHMI investigator at Stanford University School of Medicine in Palo Alto, California, who is otherwise enthusiastic about the project.

Some HHMI investigators worry that HHMI's financial commitment to Janelia could have an adverse impact on their own funding. "This is a huge money sink," says one investigator who spoke to *Science* on the condition of anonymity. "Instead, they could have appointed another 100 HHMI investigators. That would have made more sense in the current [difficult] funding climate for biomedical research."

Rubin admits that most HHMI investigators were skeptical of the project during its planning phase 5 years ago but claims that his proselytizing has turned the tide. "Gerry did a great job of bringing us around," says Nobelist Eric Kandel of Columbia University. And he says critics are missing the point: Janelia is a riskier enterprise than nurturing HHMI investigators. "Some years ago, we realized that even the investigators HHMI funds at universities tend to shy away from high-risk research," he says.

Northwestern's Morimoto and others are annoyed at what they see as Rubin's attempt to project Janelia as a much-needed alternative to academia. "It's a false statement to say that universities haven't been doing interdisciplinary science," says Morimoto. "The reason that yeast, flies, and worms have become such great biological models is that a remarkable mix of academic scientists has been working on them." He also disagrees with the notion that assured funding automatically fosters creativity. "When you are asked to write a grant [application], you benefit scientifically from having to articulate your plan," he says.

Nancy Andreasen, a psychiatrist at the University of Iowa College of Medicine in Iowa City, who chaired a 2004 National Academies' report on breaking down boundaries between fields, questions Rubin's decision to adopt what she sees as a narrow scientific mission. "I wish they had not chosen to restrict their goal to studying fruit flies and worms," she says. Andreasen also questions the wisdom of discouraging frequent travel. "I wonder how much time [Rubin] has spent on airplanes working on papers and jotting down ideas," she muses.

Rubin has ready answers to such criticism. The intellectual focus was chosen after a long selection process involving HHMI investigators, he notes, and it was essential for creating a common ground between the different research groups that the campus was seeking to attract. Understanding the neurobiology of organisms, he says, is no less broad a mission than Bell Labs' goal of developing communications technologies. Rubin plans to combat any isolationist tendencies by bringing in outside scientists for meetings and for longer, paid stints. And he sees informal peer review of ideas at weekly seminars and other internal meetings as a substitute for the vetting of grant proposals.

Roger Nicoll, a cell biologist at the University of California, San Francisco, and a member of HHMI's scientific review board, agrees that "there is a certain hubris and arrogance" associated with Janelia that could be a "turn-off" to some academics. But if the venture pays off, he says, everybody stands to gain. Nicoll expects the model to have "a trickle-down effect. … As a result of resources that HHMI is investing in Janelia, new imaging technologies and discoveries will come out of there that will benefit other researchers."

Rubin says his biggest challenge will be to keep Janelia's scientists focused on the long term even as they churn out discoveries and innovations. Group leaders will face both annual evaluations and 6-year assessments of their performance, he says, with an emphasis on the problems chosen and their collaboration with other groups rather than on the number of publications. (Group leaders who are renewed can stay on or transfer to other institutions as HHMI investigators, he notes.) In fact, Rubin says a torrent of papers could undermine the whole idea of Janelia. "If we have too many [publications]," he jokes, "I'd say our researchers aren't being ambitious enough."

–YUDHIJIT BHATTACHARJEE

CREDIT: Y. BHATTACHARJEE/*SCIENCE*

New territory. The vessel *Goor* carries researchers to a site that was off-limits during the Cold War.

ARCHAEOLOGY

A Stone Age World Beneath the Baltic Sea

As they map Germany's changing coastline, members of a research team called SINCOS are learning about settlements that were covered by water 6000 to 8000 years ago

On a warm afternoon in September, archaeologist Harald Lübke looked out from the pilot house of the *Goor*, a bright red dive boat moored 200 meters off Germany's Baltic seacoast. Three meters below the water's glassy surface, divers in bulky drysuits were excavating a prehistoric hunting camp. A deafening motor mounted on the *Goor*'s deck powered a pressure pump, which they were using to suck sediment from the sea bottom into mesh bags.

Along with sand and shells, the divers brought to the surface bones and bits of wood—debris left by ancient hunters who caught eel, fish, wildfowl, and the occasional seal. A growing body of evidence gathered by these and other undersea researchers reveals that about 7000 years ago—more than 2000 years before Stonehenge—people built fish fences, dug food-storage pits, and established sizable Stone Age communities along the shores of what appears to have been a rapidly rising Baltic.

At some point, as glaciers receded northward, the land along this coast began to sink, and over the centuries the sea moved in, submerging the hunting camps. Lübke, an archaeologist with the Mecklenburg-Vorpommern Cultural Heritage Agency, is part of a multidisciplinary German project called The Sinking Coasts: Geosphere, Ecosphere, and Anthroposphere of the Holocene Southern Baltic Sea project (SINCOS). It is trying to learn exactly how and when this landscape changed and already has determined that the water rose very rapidly, drowning the low settlements, then gradually but inexorably covering the higher ground. There's no doubt in Lübke's mind that "they must have seen the sea level rise and must have thought it wouldn't end."

Into the deep. Archaeologist Harald Lübke (*right*) watches a diver descend to an ancient hunting camp 3 meters below sea level.

CREDITS: A. CURRY/*SCIENCE*

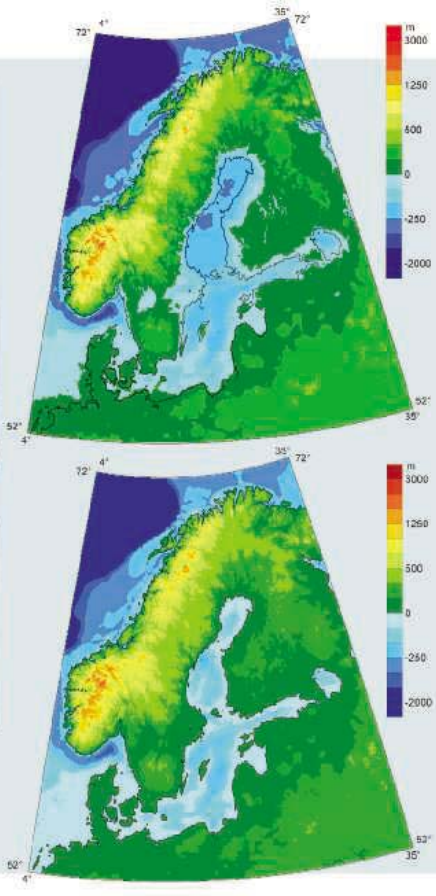
SINCOS is a "unique" collaboration linking geology, archaeology, geodesy, socioeconomics, and other fields, says Director Jan Harff. Its goal is to gather information about the Baltic coast over the past 10,000 years and, in cooperation with the Baltic Sea Research Institute in Warnemünde, also directed by Harff, to create a model that can predict future changes. Harff argues that the methods being developed here will have broad application. "Coastal retreat and erosion are so important," he says, that the approach taken in the Baltic could be useful "anywhere in the world."

Geological seesaw

Every summer, tourists come to the island of Poel, a short swim from Lübke's dive site, to sunbathe on its sandy beaches. Twenty thousand years ago, when the great ice sheets last reached their lowest latitudes, the island and nearby sea floor were frozen solid under ice at least 3 kilometers thick. The tremendous weight pressed down on the northern end of the Baltic Shield, a continental plate that includes Poel, Scandinavia, the Baltic Sea floor, and much of northern Europe. With ice sitting on the plate like a fat kid on a seesaw, the southern end, including Germany's coast, rose.

About 12,000 years ago, the world warmed up, the glaciers began to melt, and sea levels all around the world rose. As the ice sheets thinned and retreated, the pressure on the northern Baltic Shield dropped. The seesaw tipped back, lifting prehistoric beaches in northern Sweden and Finland to their present elevation 20 meters above sea level. At the same time, settlements from the same period in Germany sank deep underwater.

A channel of saltwater penetrated the land bridge between Germany and Denmark, forming the Baltic Sea out of what was once a freshwater lake, then a brackish one. But until the SINCOS project began, the timing was a mystery. Archaeological data gathered from a handful of underwater settlements are critical to determining a more precise picture of the Baltic's birth. "We wanted to find out if there was a big flood that changed everything dramatically, or if it changed step-by-step," says Friedrich Lüth, SINCOS's co-director and the head of the German Archaeological Institute's Roman-Germanic Commission. In addition to mapping the coast, the team



Corroboration. Jan Harff, with a sediment core that marks the sea's flooding into the ancient Baltic (*top right*), leading to today's coastline (*bottom right*).

wanted to learn how the people who lived here responded.

As they sort through bags of sediment for bones and wood fragments, some as small as a fingernail, Lübke's team keeps track of which sediment layers they came from (see sidebar, p. 1535). From a carbon-dating analysis of the organic fragments picked from pebbles and bits of shell, they concluded that the sea rose significantly 8000 years ago, plunging a site called Jäckelberg 3.5 meters underwater in the space of a century, and perhaps much faster. By 6000 years before the present (BP), the sea had risen another 3 meters to cover the site Lübke calls Timmendorf after the nearby village.

The project involves more than a dozen institutes in cities across Germany. Dendrochronologists from the Institute for Wood Biology in Hamburg are studying wooden artifacts and logs that are well preserved by the oxygen-poor seabed to create a continuous timeline for organic artifacts discovered in the future. They intend to tease out information about temperature and humidity to align wooden artifacts with climatic changes. And researchers at the Institute for Planetary Geodesy in Dresden and Harff's Baltic Sea Research Institute are creating computer sea-level models showing relations between temperature, melting glaciers, and sea-level rise.

Studying the ancient hunters' diet is helping to fill in the chronology. Tens of thousands of eel bones and fragments of dozens of specialized eel spears have been identified at underwater sites. Paleozoologists Ulrich Schmölke and Dirk Heinrich of Christian Albrechts University in Kiel have concluded that over the course of 2000 years, the region's inhabitants went from a diet of land mammals and freshwater fish to almost exclusively marine fish.

Evidence from drilling cores taken in deeper water tells a similar story. In a small building behind the Baltic Sea Research Institute, Harff keeps core samples covered in plastic-wrapped tubes about 10 centimeters thick. With a pen, he points out how sand and mud have been compacted in hundreds of dark, narrow bands, year after year going back millennia. Then, toward the bottom, there's a sudden change. Pulling back the plastic, Harff examines a thick, brownish layer in which he says freshwater organisms churned the sediment.

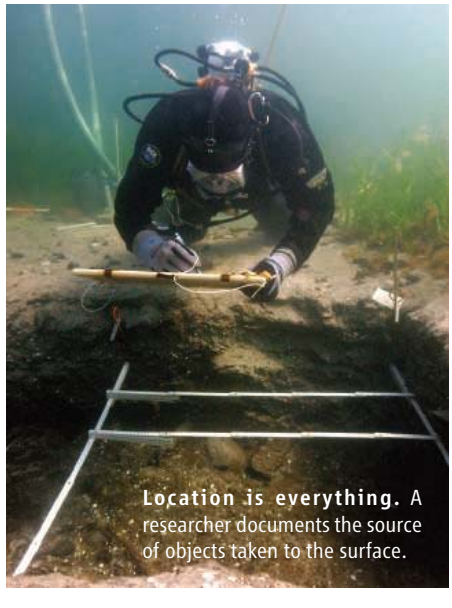
Using carbon and paleomagnetic dating, Harff's team put the freshwater layer at about 8000 years BP, or about the same time the Jäckelberg hunting camp began to be covered by rising water. Because rivers wash silt into the Baltic annually, core samples reveal regular layers during periods when the saltwater sea bottom was lifeless; these can be counted to see how many years passed. This geologic evidence agrees exactly with the date the archaeologists determined from analysis of the artifacts. "When I took this core, I was so excited," Harff says. "That we could trace back the history with such accuracy was totally unexpected."

Recently, the SINCOS project refined its estimates of timing, concluding that the Baltic rose almost 8 meters between 8100 and 5400 years BP. To some, the evidence suggests that the first 3.5 meters flooded in very rapidly, possibly within days. "It's clearer and clearer that it was a massive, sudden flood," says Lüth. "Log boats were lost, fish traps were lost—it can't have come in centimeter by centimeter." To Lübke, the evidence seems more ambiguous; he thinks the flood could have taken decades.

A Cold War ice box

The Baltic is a good place for undersea research, partly because of its history. Pinned to a whiteboard in Harff's office is a large brown index card labeled "Travel Request Form," a memento from the Cold War era. It was almost impossible to explore the Baltic before 1990, recalls Harff, who began working as a geologist in Potsdam, then part of East Germany, in 1977. Cold War politics put Baltic Sea research into a 50-year deep freeze: Until 1989, sonar scans, diving, underwater excavation, and aerial surveying were forbidden in East Germany for fear scientists would run (or swim) away.

Restrictions sometimes led to absurd scenes. In 1985, recalls Lüth, a local fisher found part of a Bronze Age spoked wheel in peat about 100 meters off the East German shore. Visiting West German archaeologists



Location is everything. A researcher documents the source of objects taken to the surface.

CREDITS: (TOP, LEFT TO RIGHT) A. CURRY/*SCIENCE*; M. MEYER, Ph.D. THESIS/GREIFSWALD UNIVERSITY (2002); (BOTTOM) HARALD LÜBKE/STATE AGENCY OF CULTURE AND CULTURAL HERITAGE MECKLENBURG-VORPOMMERN, GERMANY

were permitted to look for the rest of the wheel but forbidden to bring any equipment or look out to sea. Walking backward in swim trunks and goggles, they failed to find the site.

Yet the politics had positive consequences. Coastal development, which might have disturbed sites near shore, was nearly nonexistent. The ban on sport diving, which has resulted in the looting of underwater heritage elsewhere in the world, kept hundreds of shipwrecks safe. Ten thousand years of the region's history were almost perfectly preserved. "We knew from Danish and Polish and Swedish colleagues there were sunken ships and Mesolithic and Neolithic sites to be expected," Lüth says. "We knew something was out there, but we had no idea what it was."

"The real world—especially working at sea—began after 1990," following the reunification of Germany, Harff says. For the first time, scientists such as Harff were free to travel and meet scientists from other countries. Archaeologists and geologists dove into the virgin territory of the Baltic; they now rank it among the world's most exciting areas, says Nicholas Flemming, a British oceanographer who pioneered many underwater research techniques and is based at the Southampton Ocean Centre in the U.K. The Baltic is good for diving. And because it is isolated from the tides that churn the North Sea and Atlantic, sediments build up slowly and predictably, leaving an easy-to-read geologic record. Best of all, its cold, brackish water, low in oxygen, preserves organic materials.

Using the deep-water research vessel *Professor Albert Penck*, Harff began surveying the sea bottom in 1999 using video sleds, side-scan sonar, sediment echolocation, and core samples. His first look at the ocean floor was a revelation. Submerged forests of tree trunks and stumps lay where they fell 8000 years ago. Ancient topography—valleys, hills, river channels, inlets, and bays—could all be easily seen on sonar surveys. "It was a drowned coast," says Harff. "It was the same landscape, just underwater."

"Nirvana"

Studies of the Baltic are part of a recent wave of exploration targeting submerged prehistoric sites around the world. Ancient land bridges, huge fertile plains, and long coastlines have been submerged since the last glacial maximum, when sea levels were as much as 120 meters below where they are today.

Yet it is only recently that prehistoric underwater archaeology has begun to take off. One reason: Excavations are still expensive, slow, and risky; it may take a team of divers all day to excavate a 1-square-meter sediment layer. Another is that until recently, many archaeologists assumed that looking for underwater sites would be a waste of time because they believed that "waves would have pounded anything out of existence," says archaeologist Geoff Bailey of the University of York, U.K. But, he says, "when coastlines have convoluted features, archaeological materials may have survived." For example, it's long been assumed that the rough, storm-tossed North Sea is an archaeological wasteland. But in the past few years, archaeologists have found evidence of whole villages 11 meters beneath the water in sheltered channels near the Isle of Wight.

In the last few decades, archaeologists have found underwater prehistoric settlement sites and artifacts stretching back as much as 500,000 years near South Africa, Europe, Japan, the Middle East, the United States, and Canada. The discoveries are often made possible by interdisciplinary cooperation: archaeologists using maps of the sea bottom prepared by geologists for oil companies, for instance. Such data, added to what climate-change researchers know about sea levels, provide a new guide to how and where ancient hominids might have traveled across the now-submerged landscape. "As more academics start to get involved, the dots join together," says Southampton's Flemming. "The last 5 years, everything's been happening. If you ask me, we're heading toward nirvana."

But perhaps the greatest new resource promised by the SINCOS project, according to Lüth, is its 10,000-year data set. "Measurements of deloading from ice usually assume it's uniform, [but] there's evidence that there are local differences," says geologist William Hay of the University of Colorado, Boulder, who evaluated the SINCOS project for the German Research Foundation in 2003.

Researchers at Dresden Technical University's Geodesy Institute have constructed a computer model incorporating the data from the last 10,000 years. Lüth hopes the model will enable the team to make a reasonable attempt at predicting what's to come. There are a lot of factors involved. As sea levels rise and the Baltic's volume increases, for instance, the German coast will sink faster under the weight. "We can put it all together to give an outreach for the future," says Lüth. "The system [that] worked for the last 8000 years should work for the next 200 to 300. It could give the basis for planning and development decisions."

The SINCOS collaboration is a reminder: "We're not the only ones faced with a retreating coast," Harff says. "Our ancestors also had to leave their settlements to the ocean."

–ANDREW CURRY

Andrew Curry is a writer in Berlin, Germany.

A Hunter's Paradise

In 1999, archaeologist Harald Lübke was diving to the wreck of a medieval cog boat just off the island of Poel on Germany's north coast when he noticed flint artifacts on the ocean floor. "I dove a little deeper, and I found seven or eight flint axes in 10 minutes," Lübke recalls. It is one of about two dozen Stone Age sites identified along Germany's Baltic Sea coast since 1993.

One of the most productive is Timmendorf-Nordmole. The outlines of this hunting camp 3 meters underwater are marked by postholes and smooth stones that may have once anchored fishing fences. Divers have also uncovered a collapsed structure that may have served as an eel smokehouse or storage area. Some of the artifacts are in stunning condition, as though "they were produced yesterday," says Lübke. In 2001, he uncovered a palm-sized stone scraping tool with intact threads lashing the wood handle to the stone scraper—the first such discovery in the world. "I wasn't sure it was real when I first saw it," says Lübke.

Intact. The lashings on a stone scraper were preserved in the Baltic's chilly waters.

In addition to helping create a data set for climate and sea-level changes in the area (see main text), the artifacts have added to what scientists know about how people lived along the Baltic coast thousands of years ago. The artifacts link them to the Ertebølle cultures, which flourished in and around Denmark between 5450 and 4100 B.C.E., and fill in what had been a blank spot in the archaeological record along the Baltic coast. Lübke says the coastal settlers here remained hunter-gatherers, relying on a diet of fish, eel, birds, and seal, for centuries after people farther inland turned to agriculture. "When the ocean flooded the landscape, it created a very rich biotope," Lübke says. "It would have been like a paradise." **–A.C.**

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Getting a Read on Rett Syndrome

Scientists are beginning to find clues to how a mutated gene may cause cognitive and movement problems to appear in seemingly healthy young girls

A child's first birthday party is supposed to be a happy occasion. But that's when many parents of girls with Rett syndrome begin to notice that something is wrong with their daughters, says Carolyn Schanen, a medical geneticist at Nemours Biomedical Research in Wilmington, Delaware. In a gaggle of excited toddlers, a girl with Rett can "just seem a little flat," Schanen says. "They're not as animated; they're not as interactive." And things quickly go downhill from there.

Rett syndrome is a genetic disorder that strikes roughly one in 10,000 girls just as they are beginning to walk and talk. After developing normally for about a year, girls with the syndrome regress, losing any words they've learned as well as the ability to make purposeful movements. They end up with severe mental and physical disabilities and require full-time care.

In 1999, researchers led by Huda Zoghbi at Baylor College of Medicine in Houston, Texas, linked the devastating disorder to mutations in a gene called *MECP2* on the X chromosome. Rett syndrome is not inherited; the mutations arise unpredictably. Boys with a disabling mutation in their single *MECP2* gene often die within a year or two from respiratory failure, but girls, protected somewhat by having a good copy of the *MECP2* gene on their second X chromosome, can live into their 60s and even 70s, Zoghbi says.

In recent years, researchers have begun to understand how mutations in this single gene can cause the syndrome's variety of neurological impairments. One tantalizing lead suggests that mutations in *MECP2* derail brain development by interfering with a growth factor needed to fine-tune synaptic connections. Yet even as they grapple with the complex molecular biology behind Rett syndrome, scientists are exploring hints that the disorder, or at least some of its symptoms, may one day be treatable.

Several research teams have also recently found *MECP2* abnormalities in people with autism and related disorders, suggesting that the insights gained from studying this gene are not limited to Rett syndrome. The protein encoded by *MECP2*, called MeCP2, is normally incredibly abundant in neurons, says Adrian Bird, a molecular biologist at the University of Edinburgh, U.K., whose group discovered MeCP2 in the early 1990s. "I think we have a lot to learn biologically about what it does, and I think it's going to tell us quite a lot about the brain," he says.

Stereotypical. Girls with Rett syndrome often exhibit repetitive handwringing.

Sliding backward

Rett syndrome is especially traumatic for parents because a girl who develops it initially seems healthy, Schanen says. Most hit early developmental landmarks such as grasping objects, uttering words of the "mama" and "dada" variety, and trying to walk. But sometime between 6 and 18 months, they enter a regression phase that can last a year or more. Girls who once loved to turn the pages of a book as a parent read to them can make only stereotyped wringing movements with their hands, Schanen says. During their regression, girls often become withdrawn, anxious, and irritable. They frequently become more social later in life, but other problems persist, including profound cognitive and movement deficits and breathing abnormalities.

Hundreds of *MECP2* mutations have been associated with Rett syndrome. Some render the gene unreadable, leaving cells unable to manufacture its protein. But others cause cells to make abnormal forms of MeCP2, and still others cause cells to make too much of the protein. Remarkably, all three types of mutations cause similar symptoms. Moreover, a few published studies have linked abnormalities in the gene to other forms of mental retardation, juvenile-onset schizophrenia, and seizure disorders. At the October meeting of the American Society of Human Genetics, a team from Baylor (not including Zoghbi) reported finding *MECP2* abnormalities in 1% of a sample of autistic children. The bottom line, says Zoghbi: "This is a protein you just don't want to mess with."

How could defects in this protein or a lack of it lead to the diverse symptoms of Rett syndrome, let alone other disorders? MeCP2 is one of several so-called methyl-CpG-binding proteins, which are best known as gene silencers: They turn off genes by binding to nearby regulatory regions of DNA. Thus, one approach to unraveling Rett syndrome has focused on identifying the specific genes that would normally be turned off by MeCP2.

Several such targets have been found, but the one that has attracted the most attention so far is the gene for brain-derived neurotrophic factor (BDNF). This growth factor promotes the survival of neurons and has important roles in brain development and in synaptic changes that underlie learning and memory. "*BDNF* is *the* sexy brain gene," says Bird. "It has all the right credentials" to cause many of the problems seen in Rett syndrome. In 2003, two research teams reported in *Science* that MeCP2 normally suppresses *BDNF* expression in cultured mouse neurons (31 October 2003, pp. 885 and 890). That fit with MeCP2's proposed role as a gene silencer and suggested that mutations in its gene cause neurological problems by allowing too much BDNF to build up in the brain.

Complicating the picture, however, in the 2 February 2006 issue of *Neuron*, researchers led by Qiang Chang and Rudolf Jaenisch of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts—authors of one of the 2003 *Science* papers—reported abnormally low levels of BDNF in a strain of mice missing the mouse version of *MECP2*, called *Mecp2*. These mice exhibit several features of Rett syndrome, including reduced brain weight and hind-limb clasping, a behavior reminiscent of the repetitive handwringing in Rett girls. The same symptoms appeared when Jaenisch's team selectively disabled the

CREDIT: ALAN PERCY/UNIVERSITY OF ALABAMA, BIRMINGHAM

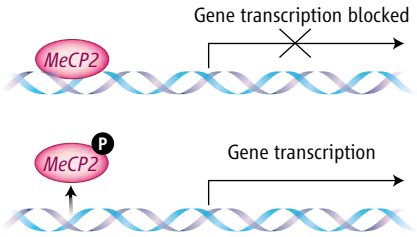
BDNF gene in the forebrains of mice. However, boosting BDNF production in mice missing *Mecp2* restored mobility and extended their life spans.

More evidence of interplay between MeCP2 and BDNF comes from a study in the 19 October 2006 issue of *Neuron* by Zhaolan Zhou and Michael Greenberg at Children's Hospital Boston and colleagues. They report that neural activity triggers a chemical modification, phosphorylation, of MeCP2 that detaches it from *BDNF*'s regulatory region, thereby turning on production of the growth factor. Preventing MeCP2 phosphorylation interfered with the protein's ability to regulate the growth of dendrites, the branches on neurons that receive synaptic connections from other neurons, the researchers also found. The findings suggest that MeCP2 is a key player in regulating gene expression in response to neural activity, Greenberg says.

In his view, the emerging picture of Rett syndrome suggests a breakdown of what neuroscientists call experience-dependent plasticity. The earliest stages of brain development, in which neurons form their initial connections, proceed largely according to genetic plans. In later stages, neural activity triggered by an animal's interactions with its environment fine-tunes neural connections, strengthening effective synapses and weeding out ineffective ones. Early life experience literally alters the brain's wiring, and Greenberg suspects that MeCP2 plays a key role in this process by regulating genes such as *BDNF*. In Rett syndrome, however, MeCP2 protein is absent or nonfunctional, and genes lose their oversight. "If you have *BDNF* and these other genes coming on at the wrong time, you're going to get miswiring of the nervous system," Greenberg says. It's no coincidence, he says, that the onset of Rett syndrome happens at about 1 year of age, a time when experience-dependent plasticity is in full swing in the human brain.

Beyond BDNF

Still, many researchers, including Greenberg, feel certain that Rett syndrome is not caused by *BDNF* abnormalities alone. Disruptions of *BDNF* and experience-dependent plasticity could conceivably account for several core features of Rett syndrome, including smaller brain size and movement difficulties, says Richard Altschuler, a neuroscientist at the University of Michigan, Ann Arbor, and research director for the International Rett Syndrome Association. "But then there are lots of other things that for parents are very much a part of Rett syndrome," including severe constipation, breathing abnormalities, and anxiety, says Altschuler, who has a daughter with the disorder.



Go time. Neural activity causes MeCP2 phosphorylation (*bottom*), allowing gene transcription to proceed.

A clue about what else goes awry in Rett syndrome appears in the 18 October *Journal of Neuroscience*. David Katz of Case Western Reserve University in Cleveland, Ohio, and colleagues report abnormal secretion of several cell-signaling molecules in mice missing the *Mecp2* gene. Katz's team first examined BDNF secretion in neurons isolated from a part of the vagus nerve involved in controlling respiration. Although these neurons have reduced stores of BDNF in 35-day-old mice missing *Mecp2*, the cells release a greater proportion of what they have.

The neurons may be trying to compensate for their low levels of BDNF, Katz says, but he suspects there's something else going on. His team also found excessive secretion in chromaffin cells in the adrenal gland. These cells release adrenaline and other compounds that mediate the body's stress response. The findings suggest that Rett symptoms such as abnormal breathing and anxiety have more to do with cells' ability to secrete signaling molecules, including BDNF, than with their ability to make them in the first place, Katz says.

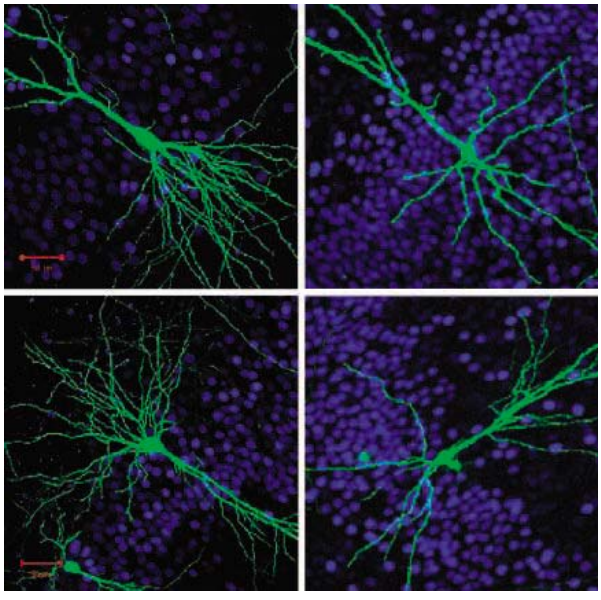
A new study by Zoghbi's team provides additional clues about Rett syndrome's anxiety symptoms. Her lab had noticed that mice with a truncated *Mecp2* gene, resulting in a malfunctioning protein, were unusually averse to handling. Zoghbi's graduate student Bryan McGill then found that the mutant mice have elevated levels of corticosterone, a stress hormone. Additional experiments revealed that MeCP2 normally suppresses the gene for corticotropin-releasing hormone (CRH), which stimulates the adrenal glands to release corticosterone and other stress hormones. In the *Mecp2*-mutant mice, the CRH gene is overactive, the researchers reported online 15 November in the *Proceedings of the National Academy of Sciences*.

Other researchers have recently reported high stress-hormone levels in the urine of girls with Rett syndrome. And given that chronic stress is bad for the brain, it's possible that correcting the overactive stress response could alleviate other cognitive symptoms of Rett syndrome, Zoghbi says. Her lab is now testing drugs that block stress hormones in *Mecp2*-mutant mice.

Bird is also investigating whether Rett-like symptoms can be reversed. He and colleagues have created a strain of mice in which the *Mecp2* gene is reversibly inactivated and can be turned back on after symptoms have developed. But even if the symptoms disappear when the gene is restored, the work won't yield a therapy for people with Rett syndrome anytime soon—the sophisticated genetic tricks used in the mice aren't available yet in humans.

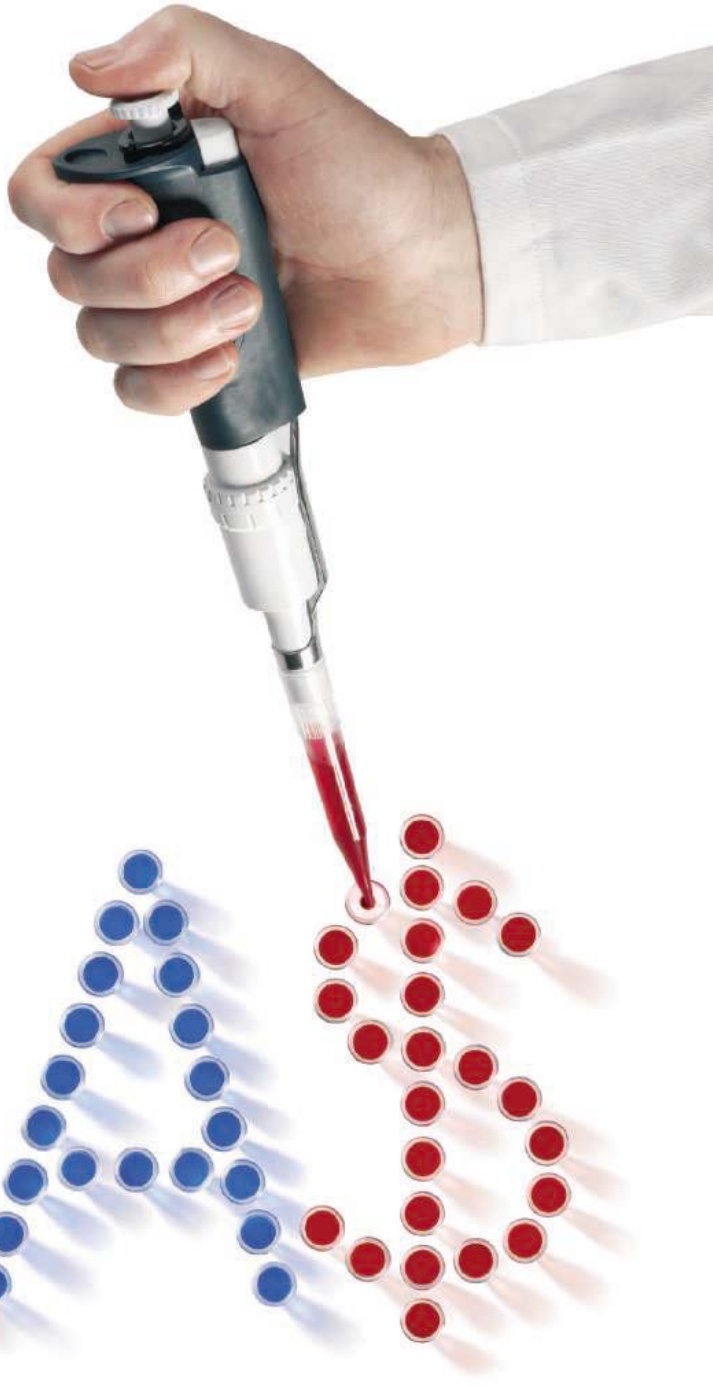
Even so, many researchers express optimism that girls with Rett syndrome have substantial numbers of healthy neurons that can form working circuits if coaxed in the right way. Based on her clinical experience, Schanen says it's something she has long suspected. "My interest in Rett syndrome started because when I looked at these little girls, it wasn't like the lights are on and nobody is home; it's like the lights are on, there's somebody in there, and I just can't get them to come to the door."

–GREG MILLER



Stunted branches. Mouse hippocampal neurons (green) grow dendrites with fewer branches when MeCP2 is blocked (*right*) compared to when the protein is active (*left*).

CREDITS (TOP TO BOTTOM): P. HUEY/*SCIENCE*; Z. ZHOU *ET AL.*, *NEURON* **52**, 255 (2006)



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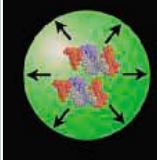

LETTERS

edited by Etta Kavanagh

Deciding Who Should Get the Flu Vaccine

THE POLICY FORUM "WHO SHOULD GET INFLUENZA VACCINE WHEN not all can?" by E. J. Emanuel and A. Wertheimer (12 May, p. 854) has initiated a welcome debate on ethical considerations during a pandemic. However, the authors' proposed guiding principle for allocating vaccine in a situation of scarcity—the "investment refinement of life-cycle principle including public order" or IRPOP—gives rise to some serious problems.

Emanuel and Wertheimer weigh the investments a person has made in her life balanced by the amount left to live, i.e., the amount of unfulfilled potential. The authors conclude that this would favor people aged 13 to 40 years old. However, in most societies, there is a great difference in both life prospects and life expectancy in different social groups (*1*). For instance, a white 16-year-old teenage boy in the United States has on average a 77% chance of reaching age 65, while an African-American teenager from Harlem, New York, has only a 37% chance (*2*). Taking the IRPOP principle seriously, we should not give the "socially challenged" black youngster a high priority for vaccination. This would, of course, perpetuate existing injustices. We can always claim that all 16-year-olds ought to have the same life expectancy and vaccinate them equally, but then we have disregarded the investment principle and are back to the unrefined but egalitarian life-cycle principle.

No man is an island. To invest, you usually expect returns, and to realize your own interests, hopes, and plans, you usually have to realize someone else's too. Even though this was not an aim of the IRPOP principle, the effect of favoring those with the potential to realize their interests, hopes, and plans would be to favor those who are most profitable. We are then giving provisions for activities that uphold vaccine production, health care, or public order and economic profitability in general. That the chronically unemployed should get a lower priority for vaccination than those who have a job would in most societies be quite unacceptable. We have to find other and more equitable grounds for prioritizing than realizable life investments.

What are the characteristics of people between adolescence and middle age, besides having unfulfilled lives and being most productive? They are also those taking the highest risks in life (probably just because they have these unfulfilled hopes). Perhaps some of them are also willing to take the risk of acquiring influenza to let someone else get vaccinated first. Not only self-interest but also willingness to sacrifice your own interests for others give weight to ethical considerations. To endorse a principle that prioritizes individual resources and not some aspect of the common good would probably offend many, were they asked. So that is precisely what we should do. Go and ask.

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Response

ONE AIM OF THE INVESTMENT MODIFICATION of the life-cycle principle was to present a clear alternative to two principles for the allocation of influenza vaccine in a pandemic: (i) save the most lives, which would give higher priority to the elderly, and (ii) a pure life-cycle principle (or save the most life years), which would give higher priority to the youngest infants. We were aiming to advance a principle that is committed to the equal worth of all persons and yet recognizes morally relevant distinctions among them.

Holmberg charges that we would favor the "most profitable." We did not articulate every ethical principle relevant to this issue, mainly because we assumed that they would operate within a more general framework that includes such principles as no racial and no sexual discrimination. Hence, the investment modification principle gives higher priority to a white adolescent than a white infant; we reject giving higher priority to a white adolescent than a black adolescent or a girl over a boy.

Although society might benefit more from saving the more productive than the less productive, that is not the sort of "investment" that is embedded in the investment modification of the life-cycle principle. The investment in youths is from childrearing, education, love, and attention, and their own efforts at self-development; the "return on investment" is more in the way these people at age 20 or so can then develop and realize their life plans. This is something that can be, if not fully realized, then progressively realized after age 20 or so. Much will be fulfilled before 65. This gives a reason to give priority to all adolescents, not only those who have a higher likelihood of living until 65. We thought we made this clear when we rejected the World Health Organization's disability-adjusted life years (DALYs) with its prioritization based on those who are "contributing to the well-being of others" through earning power or caregiving.

Finally, we do not understand how Holmberg would want to give weight to the "common good" as opposed to individuals. If some-

one wants to forego receiving a vaccine for the sake of the common good, he can always do so.

Doubtless, any principle of rationing will offend many. We think it unlikely that this is an issue that can be fruitfully resolved by a referendum or public opinion poll, and so although we would welcome a lively debate, we think that policy-makers must assume the responsibility of producing the principles that are most ethically defensible.

EZEKIEL J. EMANUEL AND ALAN WERTHEIMER

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The Cost of Access to HIV Treatment

OUR RESEARCH (*1*) CATALOGED ALL RANDOMized, controlled trials of interventions for HIV/AIDS that were conducted in Africa from 1987 to 2003. We identified 77 trials overall; of these, only 10 were testing approaches to HIV/AIDS prevention. After reading the exchange "HIV research and access to treatment" by M. Warren and "Response" by R. M. Grant *et al.* (Letters, 13 Jan., p. 175), we attempted to quantify the number of seroconversions occurring in the 53,144 participants included in all 10 trials. Trials were conducted in seven countries and differ in terms of length of follow-up, participant risk profile, and seroconversion rate, presenting a challenge to economic modeling. At an estimated overall annual seroconversion rate of 2.5% and using the numbers from these trials, we estimate that 1329 people would contract the virus each year.

Because cost-effectiveness data are limited, we used data from a recent South African study (*2*) measuring the cost of antiretroviral (ARV) provision (including monitoring, related care, and hospital inpatient days, but excluding indirect costs) to estimate the costs of treating 1329 seroconverted participants. At current South African public-sector costs of $1342 per person per year, annual provision of antiretroviral treatment to all participants would cost $1,783,518. At anticipated public-sector prices for locally manufactured drugs, per-person per-year costs would drop to $793, reducing the overall costs for all those seroconverting to $1,053,897. These annual costs are modest and would remain so even if doubled or tripled to account for longer durations of follow-up and for potentially higher costs for small numbers of treatment cohorts or for areas whose treatment costs may exceed those of South Africa.

Costing out the expenses associated with providing ARV treatment to those who seroconvert reveals the weakness of arguments suggested by Grant *et al.*, that offers of "a lifelong guarantee of treatment could exhaust limited research resources and does nothing for those who elect not to participate in research." If ARV treatment costs are as modest as we project (and we strongly recommend that formal cost analyses be done), sponsors of clinical HIV research can surely afford to provide the additional resources necessary to ensure ARV treatment to those who seroconvert during trials. Providing this benefit will also protect those who do not participate in research, because persons receiving supportive ARV treatment and associated care will be less likely to transmit their infection to others in their communities.

PAUL GALATOWITSCH[1] AND NANDI SIEGFRIED[2]

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3. The authors are grateful to Ruanne Barnabas and Timothy Law Snyder for their comments on an earlier version of this letter.

Response

WE ADVOCATE STRENGTHENING TREATMENT programs for all people, including those who seroconvert during prevention trials. The Global Fund, PEPFAR, and other treatment programs currently receive substantial funding from sponsors who also support prevention research. Long-term HIV care for people who become infected during HIV prevention trials is not the moral obligation of researchers (*1*), any more than long-term treatment of cardiovascular events is the moral obligation of investigators in primary prevention trials of cardiovascular disease.

HIV infection has not been an adverse event of prevention study participation. Rather, HIV infection arises from behaviors and circumstances that continue despite provision of the best prevention services, which are provided to all study participants. Importantly, reported risk behavior routinely decreases during prevention studies, including HIV vaccine trials (*2*) and chemoprophylaxis, whether post-exposure (*3*, *4*) or pre-exposure (*5*).

Contrary to the authors' assertion, the annual cost of treatment cited would dwarf prevention research budgets when multiplied out to lifelong commitments. According to their calculations, provision of antiretroviral treatment for newly infected participants in current trials alone would cost $1,783,518 or $1,053,897 annually. Because treatment will need to be sustained lifelong once begun, the total cost is in fact more than 20 to 30 times this amount. Additionally, we can anticipate a minimum of 8 to 10 new HIV prevention efficacy trials beginning enrollment in the next 2 to 3 years, including evaluation of microbicides, pre-exposure prophylaxis, and vaccines. Prevention research resources are barely sufficient to pay for the costs of the research, which includes provision of standard prevention for all participants, medical evaluation, safety laboratory testing, HIV testing, recruitment, retention, and community education and participation. In many places, research monies are used to treat sexually transmitted infections and adverse events related to study participation.

Diverting prevention research funds to treatment programs would limit the speed with which promising prevention strategies can be evaluated and more infections averted. Additional ethical and logistical issues would arise from requirements that researchers take primary responsibility for ensuring that treatment is available for trial seroconverters, rather than helping to strengthen treatment programs for everyone. Would this coverage extend to persons found to be infected before enrollment? To persons who become infected after the trial ends? Would treatment for spouses/partners be available, and if not, would drug sharing occur? How would care be provided to those who move away? Because the majority of HIV care is required many years after seroconversion, new financial mechanisms would be needed to assure funds were available when needed. These financial mechanisms would provide no benefit to people with HIV who need treatment now, nor to those who choose not to participate in research.

Effective prevention is the only hope for sustainable universal treatment. Success in the fight against AIDS depends on mutually enabling cooperation between prevention and treatment advocates.

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

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Responding to Amphibian Loss

IN THEIR POLICY FORUM "CONFRONTING amphibian declines and extinctions" (7 July, p. 48), J. R. Mendelson III and colleagues offer a strategy for "stopping" the widespread losses of frogs, toads, and salamanders. Disease research and captive breeding figure prominently in their call for action.

Mendelson *et al*. imply that the main challenge, apart from curbing "familiar threats" such as habitat destruction, lies in combating the chytrid fungus *Batrachochytrium dendrobatidis*. This pathogen may well be a central proximate cause of mortality, but we question the belief that it spreads gradually across large regions, spelling doom for amphibian communities wherever it arrives (*1*–*4*). The observations that ostensibly support this "extinction-wave" model are open to interpretation, and the chytrid inhabits many places where major losses have not been observed (*5*–*8*). Furthermore, evidence suggests that climate change and other factors may contribute to declines by triggering disease outbreaks, which might travel varying distances in wavelike patterns (*9*–*12*). In any case, many populations survive such episodes (*13*) yet face an uncertain future as environments deteriorate, regionally and globally.

Protecting populations in centers for captive breeding may evoke Noah's ark. In reality, these centers would be high-tech lifeboats, costly and of uncertain design, afloat indefinitely on perilous seas. Of the species that would obtain the inevitably limited seats, how many would make it home again, or have a home worth returning to? Of course, some captive breeding is worthwhile, especially for research and education, but its efficacy in preserving nature should not be oversold.

There is no substitute for putting the Earth on a safe path. The Amphibian Conservation Action Plan recognizes this—stating, for example, that global warming must be addressed, and proclaiming amphibians "canaries in the global coal mine" (*14*). Mendelson *et al*., however, say nothing about stemming environmental deterioration (besides habitat loss) and would instead put the canaries under intensive care. To suggest that this alone can halt the extinctions undermines scientific credibility and engenders false hope and complacency among voters and consumers.

Biodiversity loss warns that humanity's life-support system is crumbling. Those who realize this may become responsible global citizens, demanding sound governance and accountability. Through outreach, we must foster an international "war on environmental deterioration" with initiatives on the scale of the Manhattan and Apollo projects. Society faces critical choices, and the clock is running.

J. ALAN POUNDS,[1]* ANA CAROLINA CARNAVAL,[2] ROBERT PUSCHENDORF,[3] CÉLIO F. B. HADDAD,[4] KAREN L. MASTERS[5]

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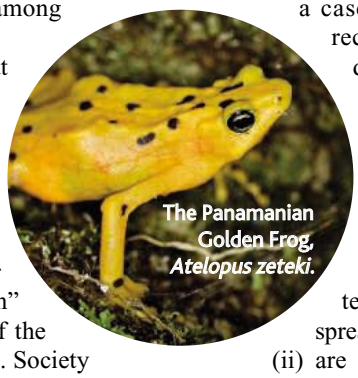
Response

THE AMPHIBIAN CONSERVATION ACTION Plan (ACAP) reflects the need for a global, comprehensive response to amphibian extinctions and is a consensus position reached by 76 international scientists and conservationists (including two of the Letter's authors, Pounds and Carnaval).

Our Policy Forum identified chytridiomycosis [caused by the fungus *Batrachochytrium dendrobatidis* (*Bd*)] as a case study because of its recent emergence, global distribution, and ability to cause extinction. We argued that captive husbandry is a necessary and timely response to this threat.



The Panamanian Golden Frog, *Atelopus zeteki*.

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Pounds *et al.* (i) disagree with some spatiotemporal dynamics of *Bd* spread, not mentioned by us; (ii) are skeptical about captive breeding programs; and (iii) suggest that a focus on captive breeding would distract from other solutions to amphibian extinctions.

Pounds *et al.*'s citations (*1*–*4*) do not support their statement that where chytrid fungus is present, there are no major declines because these articles all report declines potentially attributable to chytridiomycosis. The loosely worded statement that "many populations survive such episodes" misrepresents the severity of declines. Strong evidence demonstrates that *Bd* is one of the few diseases capable of causing extinction of species (*5*), not just population extirpation. Nevertheless, we readily acknowledge instances where *Bd* was detected but where amphibian populations were little affected (*6*).

Pounds *et al.* exaggerate our focus on captive programs and suggest that captive programs "engender false hope and complacency among voters and consumers," yet they offer no empirical support for these claims or provide alternative actions. Captive programs are a single tool representing a case-specific response that can forestall extinctions (*7*). Control of *Bd* in the wild is not currently possible, but it is likely to continue causing extinctions of amphibians; these realities warrant captive assurance colonies as a last resort for species

endangered by this disease.

We did not say that conservation should focus solely on chytridiomycosis, nor rely solely on captive programs. We endorse the ACAP Declaration, which clearly provides research and conservation priorities for all threats to amphibians.

We disagree with the vague call to reverse environmental deterioration "[t]hrough outreach" as a solution to amphibian extinctions. First, dealing with both the proximate and ultimate causes of amphibian extinctions is the most effective strategy. Pounds *et al.* seem to think that only addressing ultimate causes will prevent ongoing extinctions, but we disagree because many amphibians will go extinct before the global environment responds (*8*). Second, focused, forward-thinking plans are encouraging to the general public, policy-makers, and donors. Since publication of our Policy Forum, the ACAP has received endorsement from IUCN, unsolicited gifts from foundations, queries from the public, and coverage in the popular media. This attention broadly supports amphibian conservation, not specific causes or programs.

Both groups agree that "war on environmental deterioration" would address the amphibian crisis, and that the clock is running, but even under the best-case scenario, that is a decades-long project, during which time many additional species may be lost (*9*). Our Policy Forum and ACAP offer specific, large-scale, immediate responses to conserve amphibians.

JOSEPH R. MENDELSON III,[1]* KAREN R. LIPS,[2] JAMES E. DIFFENDORFER,[3] RONALD W. GAGLIARDO,[4] GEORGE B. RABB,[5] JAMES P. COLLINS,[6] PETER DASZAK,[7] ROBERTO IBÁÑEZ D.,[8] KEVIN C. ZIPPEL,[9] SIMON N. STUART,[10] CLAUDE GASCON,[11] HÉLIO R. DA SILVA,[12] PATRICIA A. BURROWES,[13] ROBERT C. LACY,[14] FEDERICO BOLAÑOS,[15] LUIS A. COLOMA,[16] KEVIN M. WRIGHT,[17] DAVID B. WAKE[18]

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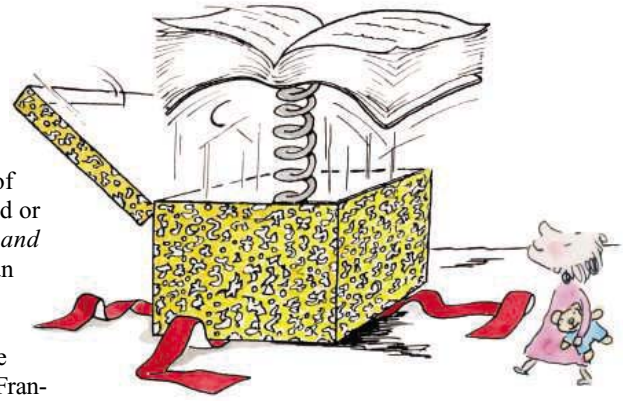
FOR YOUNGER READERS

Science Books for Fun and Learning—Some Recommendations from 2006

If your holiday gift lists include children or young adults whose interest in science you are trying to encourage, we offer as suggestions the finalists for the 2007 *Science Books and Films* Prizes for Excellence in Science Books. The prizes are intended to honor books that promote an understanding and appreciation of science in younger readers. Sponsored by the AAAS and Subaru, they are awarded in four categories: children's science picture book (for readers in grades K–4), middle grades science book (grades 5–8), young adult science book (high school), and hands-on science/activity book (any age). The titles considered for the 2007 prizes were published between September 2005 and August 2006.

Here we present our short descriptions of the 17 finalists chosen by panels of librarians, educators, and scientists. Full reviews of each book have been published or will appear in *Science Books and Films*, and AAAS members can read these reviews on the Web. The four winners for 2007 will be announced at the AAAS Annual Meeting in San Francisco in February.



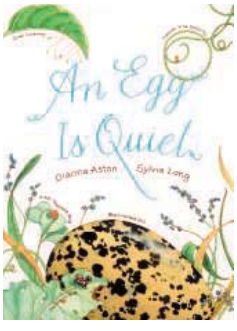
The criteria for evaluating the books include a clear and accurate presentation of scientific concepts. But we join the judges in hoping that the finalists will entice young readers to turn to science books for enjoyment as well as for information.

–Heather Malcomson,[1] Barbara Jasny, and Sherman Suter

Children's Science Picture Book

Boy, Were We Wrong About Dinosaurs! Kathleen V. Kudlinski, with illustrations by S. D. Schindler. Dutton Children's, New York, 2005. 32 pp. $15.99. ISBN 0-525-46978-8.

Demonstrating how scientific knowledge grows as new facts become known, the author and the illustrator present once-common ideas about dinosaurs that have been overturned or called into question. Among their examples are the thumb spike of Iguanodon, posture, coloration, skin covering, maternal behavior, and the evolutionary fate of these extinct animals that have long fascinated children.

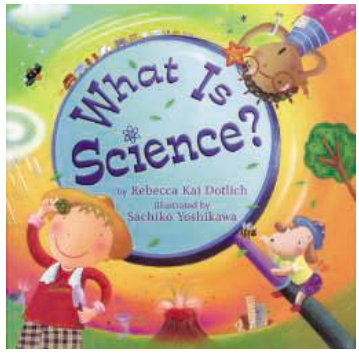


An Egg Is Quiet. Dianna Aston, with illustrations by Sylvia Long. Chronicle, San Francisco, 2006. 30 pp. $16.95. ISBN 0-8118-4428-5.

Striking and accurate drawings of all types of eggs—from the very tiny blue crab egg to the hefty ostrich egg—bring this book to life. The beautiful illustrations and simple yet informative text show why eggs are different shapes (seabird eggs are pointy at one end, so they roll around in safe little circles, not off the cliff), colors (to camouflage themselves), and textures (amphibian eggs are "gooey", which keeps them from drying out). The author excellently captures the incredible variety of eggs while celebrating their form and function.

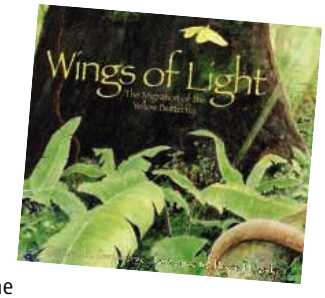
Marvelous Mattie. How Margaret E. Knight Became an Inventor. Emily Arnold McCully. Farrar, Straus, and Giroux, New York, 2006. 32 pp. $16. ISBN 0-374-34810-3.

Charmingly written and illustrated with watercolors, this book tells about the life of the inventor Margaret E. Knight. As a girl in the 1800s, she kept a book of drawings called "her inventions" and designed improvements to the machines she worked with in factories that improved their efficiency and helped keep workers safe. She confronted prejudice against women and won a patent for a paper bag–making machine that enabled her to go into business for herself. The story is one both girls and boys can enjoy.



What Is Science? Rebecca Kai Dotlich, with illustrations by Sachiko Yoshikawa. Holt, New York, 2006. 32 pp. $16.95. ISBN 0-8050-7394-9.

Naturally curious about the world around them, children love to ask questions. To spark interest in science, this delightful book encourages them to do just that. A group of inquisitive children and their dog explore the exciting world of science through a variety of activities such as visiting an oilfield, twirling in a hurricane, flying a spaceship to Saturn, biking through the mountains, looking at the stars, and more. Young readers will relish the whirlwind tour that encompasses stars, planets, rocks, soil, sea and sky, hurricanes, volcanoes, earthquakes, and snow. The bright, bold illustrations will cause children to reach for the book on their own.



Wings of Light. The Migration of the Yellow Butterfly. Stephen R. Swinburne, with illustrations by Bruce Hiscock. Boyds Mills, Honesdale, PA, 2006. 32 pp. $15.95. ISBN 1-59078-082-5.

Brilliant watercolors and a lyrical text tell the story of the cloudless sulfur butterfly's migration from the Yucatan Peninsula up the coast of North America to New England. Young readers

[1]*Science Books and Films*, 1200 New York Avenue, N.W., Washington DC, 20005, USA. E-mail: hmalcoms@aaas.org

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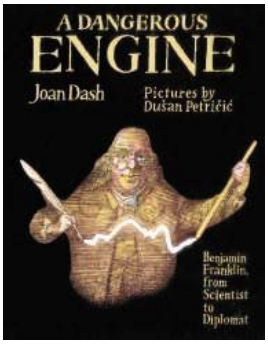
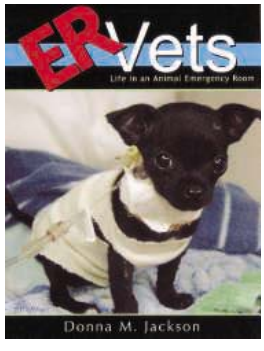
will fly alongside the butterflies as they sail above the Yucatan rain forests, over the Gulf of Mexico, and on to land again in the southern United States. The story is nicely personalized by the book's focus on a single butterfly "with a notch in its wing"—a thoughtful middle ground between an excessively abstract description of the whole population and the alternative of cutesy anthropomorphism so often seen in young children's insect books.

Middle Grades Science Book



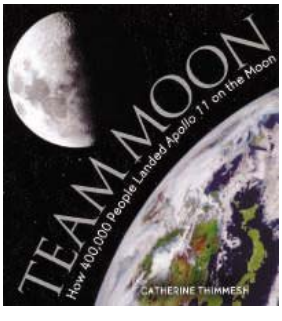
A Dangerous Engine. Benjamin Franklin, from Scientist to Diplomat. Joan Dash, with illustrations by Dušan Petričić. Farrar, Straus, and Giroux, New York, 2006. 256 pp. $17. ISBN 0-374-30669-9.

Franklin's love of science and invention are the focus of the first half of this informative and entertaining biography. Here the author discusses Franklin's experiments (and pranks) with electricity, observations of marine life and the Gulf Stream, correspondence with European scientists, and creation of such devices as flippers for faster swimming, bifocals, a lightning rod, a glass harmonica, and the stove later named for him. The remainder of the book covers Franklin's long sojourn as a diplomat in London and then France and his eventual return to America and participation in the Constitutional Convention.



ER Vets. Life in an Animal Emergency Room. Donna M. Jackson. Houghton Mifflin, Boston, 2005. 66 pp. $17. ISBN 0-618-43663-4.

Many children when asked what they want to be when they grow up will reply, "a veterinarian!" This book will further develop their interest in veterinary medicine. Filled with full-color, behind-the-scenes photographs, it captures the drama and excitement of an animal emergency room. The author provides a brief history of veterinary medicine as well as accounts of real-life pets and their treatment at the animal hospital.

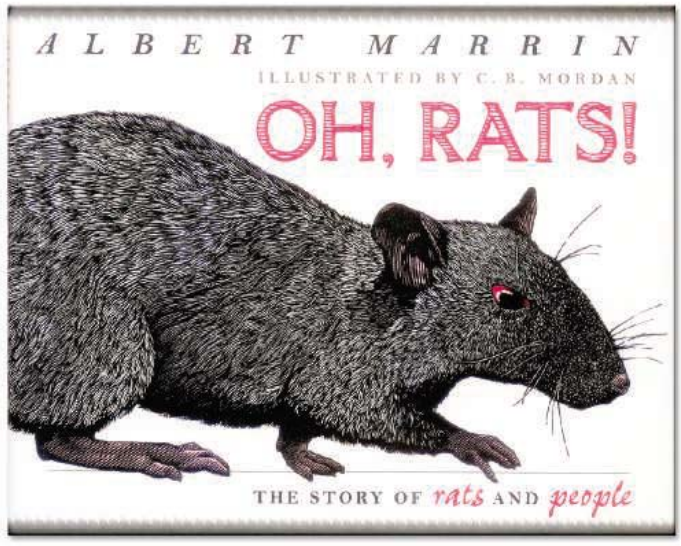


Team Moon. How 400,000 People Landed Apollo 11 on the Moon. Catherine Thimmesh. Houghton Mifflin, Boston, 2006. 80 pp. $19.95. ISBN 0-618-50757-4.

This book takes readers behind the scenes of the mission that first placed humans on the Moon—dramatically telling, for example, the story of the near-catastrophe the astronauts faced when they were less than 35,000 feet from the lunar surface. The pictures do the story full justice, and it was good to see the emphasis on the team who made an historic event possible.

Oh, Rats! The Story of Rats and People. Albert Marrin. Dutton Children's, New York, 2005. 48 pp. $16.99. ISBN 0-525-47762-4.

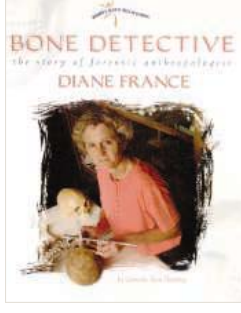
To many, rats are pesky pests: voracious consumers of our foods and garbage and spreaders of contagion and disease. To some, they are menu



items. And to others, they are intelligent and sociable critters that make ideal pets. Surveying many facets of the relations between rats and people, the author enlivens his account with enticing vignettes. While some readers will be more receptive to "Getting Rid of Rats" than to "Rats to the Rescue," all should appreciate this intriguing account and its accompanying illustrations.

Young Adult Science Book

Bone Detective. The Story of Forensic Anthropologist Diane France. Lorraine Jean Hopping. Joseph Henry, Washington, DC, 2005. 128 pp. Paper, $9.95. ISBN 0-309-09550-6. Women's Adventures in Science.

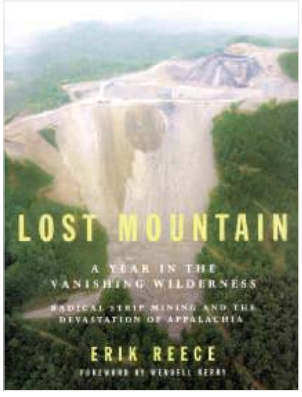


The book starts by capturing a humorous day in the life of Diane France as she walks in the heels needed for a conference while transporting (more or less successfully) a brain in a bucket full of formalin. The author then paints an engaging picture of France's youth and adolescence in a small town in Colorado and her subsequent education. The book also presents fascinating descriptions of some actual forensic anthropology cases. It conveys France's spirit of adventure but does not leave out emotionally painful aspects of her work or difficult parts of her life. Readers will learn about the science and may well be inspired by France's motto, "If you have really good adventures, then you've had a good life."

Cool Stuff and How It Works. Chris Woodford *et al.* DK, New York, 2005. 256 pp. $24.99, C$32.99 ISBN 0-7566-1465-1.

Teens who enjoy taking "stuff" apart in order to find out how it works will spend hours poring over this eye-opening book. The book's carefully worded descriptions, colorful graphics, and clear fonts and line spacing help the reader more easily understand today's modern tools. Using cutting-edge imaging techniques, the authors dissect everyday items, such

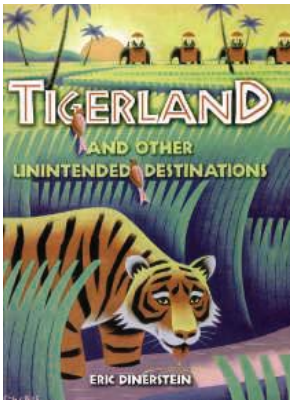
as digital cameras and video games, to unravel their inner workings.



Lost Mountain. A Year in the Vanishing Wilderness. Radical Strip Mining and the Devastation of Appalachia. Erik Reece. Riverhead, New York, 2006. 269 pp. $24.95. ISBN 1-59448-908-4.

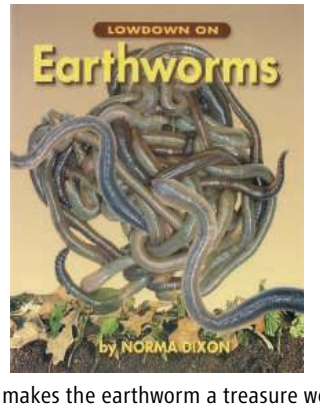
The author spent a year watching the effects of strip mining on Lost Mountain in Kentucky. His investigative reporting produced a story in Harper's that won a 2005 Columbia University School of Journalism award for distinguished environmental journalism. This book, based on that story, is a passionate outcry against the devastation of a beautiful region, the effects of strip mining on the local population, and the indifference of the coal industry.

Tigerland and Other Unintended Destinations. Eric Dinerstein. Island, Washington, DC, 2006. 288 pp. $25.95. ISBN 1-55963-578-9.



Through a series of autobiographical essays, the author recounts his efforts to preserve wildlife and wildlands. He describes his not-always-enjoyable adventures seeking tigers in Nepal, giant river otters on the Orinoco, snow leopards in Kashmir, and bats in Costa Rica's Monteverde cloud forest. There are encounters with wildebeest on the Serengeti, the ancient vegetation of New Caledonia, prairie dogs and bison on North America's Great Plains, and the fauna and flora (endemic and introduced) of the Galápagos. Woven into his narrative are portraits of environmentalists and considerations of critical conservation issues such as ecotourism, habitat fragmentation, and ecosystem restoration. The book provides a quiet yet compelling introduction to conservation biology.

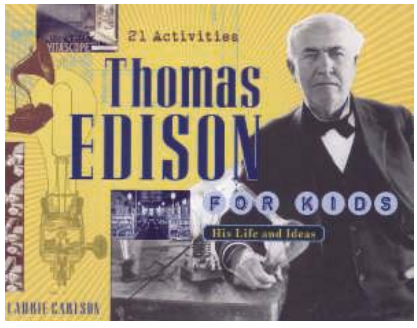
Hands-On Science/Activity Book



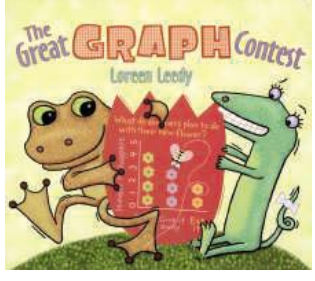
Lowdown on Earthworms. Norma Dixon. Fitzhenry and Whiteside, Markham, ON, Canada, 2005. 32 pp. $16.95, C$19.95. ISBN 1-55005-114-8.

There are few greater pleasures for a child than digging in the dirt, and this book makes the earthworm a treasure well worth hunting for. The author provides very readable discussions of the importance of these "humble heroes" and of their anatomy, habitats, and behavior. Readers will also find several experiments they can carry out themselves and easy-to-follow instructions for making a see-through wormery.

Thomas Edison for Kids. His Life and Ideas, 21 Activities. Laurie Carlson. Chicago Review Press, Chicago, 2006. 160 pp. Paper, $14.95, C$20.95. ISBN 1-55652-584-2.



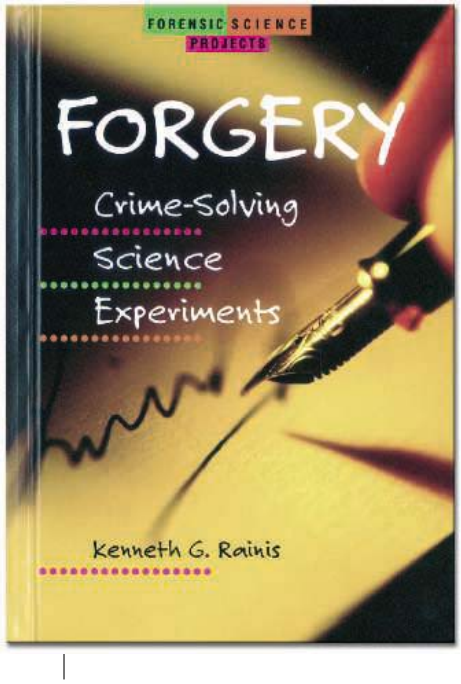
The author uses the life and inventions of Thomas Edison to inspire a new generation of curious minds. Young readers will find an excellent introduction to the relations among science, technology, and society. That perspective on the history and nature of science provides the backdrop for descriptions of Edison's curiosity, experimentation, inductive reasoning, and many inventions. Each chapter in the chronological narrative is strengthened by the inclusion of two or three related hands-on activities. For example, students can build a simple circuit to test various materials for electrical conductivity.



The Great Graph Contest. Loreen Leedy. Holiday House, New York, 2005. 32 pp. $16.95. ISBN 0-8234-1710-7. Paper, 2006. $6.95. ISBN 0-8234-2029-9.

In this colorful book for young elementary school students, a toad and a lizard compete to make the best graphs. They explore using tallies and surveys to gather data and a variety of means of presenting their findings: quantity graphs, pie charts, Venn diagrams, and bar graphs. The final pages provide details about the graphs and suggest activities.

Forgery. Crime-Solving Science Experiments. Kenneth G. Rainis. Enslow, Berkeley Heights, NJ, 2006. 128 pp. $31.93. ISBN 0-7660-1961-6. Forensic Science Projects.



This book is aimed at the young detective in your family. It presents ten cases—based on actual forgeries that were solved through forensics—including descriptions of the "scoundrels," their crimes, and their punishments. Each case is paired with a project that introduces the reader to a different forensic technique—such as chromatography, handwriting analysis, and watermark identification. Parental supervision is required for some of the projects. Like the other titles in its series, the book can provide many hours of crime-solving enjoyment.

10.1126/science.1137746.

FICTION

Armageddon in the Oceans

Boris Worm

"Worms. Monsters. Methane. Natural disasters. It was time for a drink." This is how marine biologist Sigur Johanson sums up the state of the planet just days before all hell breaks loose in Frank Schätzing's eco-thriller *The Swarm*. Following disaster movies such as *The Day After Tomorrow* and *The Core*, the book focuses on a global threat set to end human civilization. Only this time, it comes from the depths of the ocean, and some of the book may be closer to reality than we would like.

Initially, the threat builds slowly. Fish and whales disappear. Invasive species foul ship hulls. Jellyfish and toxic blooms appear more frequently and in unusual places. This probably sounds familiar. Indeed, these are the usual reports from an ocean that is being transformed on a global scale. While I am typing this, I look out on the Northwest Atlantic—one of the most overfished regions of the world (*2*). I am reminded of my university years on the Baltic, where I studied noxious algal blooms that spoiled beaches. And I think of the formerly fish-rich Benguela upwelling system off Namibia, which is now dominated by millions of tons of jellyfish (*3*), and the many other locations heading toward similar fates (*4*, *5*).

Overall, these changes are gradual and, for most of us, difficult to see. However, there is a real concern that complex marine ecosystems can shift suddenly and catastrophically (*6*). In *The Swarm*, the rate of change is sped up by a few orders of magnitude, we get fast-forwarded into some of the scarier scenarios for our planet's future, and we must face the several environmental crises simultaneously: a rapid spindown of the Gulf Stream and Atlantic deep-water circulation, destabilization of methane hydrates on the sea floor, toxic seafood, and deadly dinoflagellate blooms, among others.

The global consequence is an ocean that turns deadly. People living near the coast have to flee inland. The shipping, fishing, and tourism industries grind to a halt. The ocean becomes a no-go zone. In painting these scenarios, however exaggerated they may be, the author manages to show the reader how intimately our lives and well-being are linked to the ocean—and how our landlubbing species is often happy to ignore changes in the seas, until it is too late.

Scientists feature prominently in this story as the only characters who are thinking about the big picture. They are the canaries in the coal mine, the main defenders against the enemy that is our own ignorance. Yet, they are also shown to be slow to communicate their results, usually waiting for absolute certainty.

At one point in the story, marine scientist Heiko Sahling warns, "We don't have time to leave anything to anyone [else]…. We know exactly what is going to happen." But by then it is too late to stop the massive blowouts of methane gas that later trigger a tsunami in the North Sea.

In another scene that resonated with me, science journalist Karen Weaver discovers that the global circulation pattern is collapsing. She only sees the extent of the problem when the military gives her unlimited access to global satellite data, which has been combined to "form the complete history of oceanic mapping." She muses that "[p]roving the existence of global changes meant obtaining data on a global scale." I agree. This is what emerges as the most interesting message from the book: that the oceans are changing on a global scale, that our understanding of these changes always lags behind them, and that too often we are too slow, too conservative, or simply too unimaginative to put all the pieces together.

The Swarm
A Novel of the Deep
by Frank Schätzing

Translated from the German (*1*) by Sally-Ann Spencer. ReganBooks (HarperCollins), New York, 2006. 893 pp. $24.95, C$32.50. ISBN 0-06-081326-1. Paper, Hodder and Stoughton, London. £12.99. ISBN 0-340-89523-3.

In preparing to write this novel, Schätzing (a marketing executive in Cologne who has written several successful historical crime novels) spent several years researching marine issues and talking to scientists, and his efforts show. Not only entertaining, the book is also packed with interesting facts about topics ranging from whale behavior to marine geology. Even some of his protagonists (such as Sahling, with whom I spent my undergraduate years) are real people; others are pure fiction. Similarly, while some of the story is based on real information, most is complete fabrication. My biggest concern is that it is almost impossible to disentangle where the facts end and the author's imagination takes over. Yet, this mixture has been hugely successful in raising people's awareness and interests in the oceans. The book has sold millions of copies in Europe and has reportedly led to large increase in the profile (and funding) of marine science in Germany, where it was first published.

For me, *The Swarm* only drags in the last few chapters, when the action-adventure bit takes over and the science goes completely overboard. The ensuing battle between good and evil finds scientists and the military racing to apply their contrasting "cures" to the world's problems. Will the oceans be saved? Will reason—finally—prevail? The answers are available in a bookstore near you.

They came from the deep. The Spanish-flagged bottom-trawler *Ivan Nores* hauled these fish up from the depths of the North Atlantic Ocean.

CREDIT: KATE DAVISON/GREENPEACE

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RESEARCH AND DEVELOPMENT

Where Is the New Science in Corporate R&D?

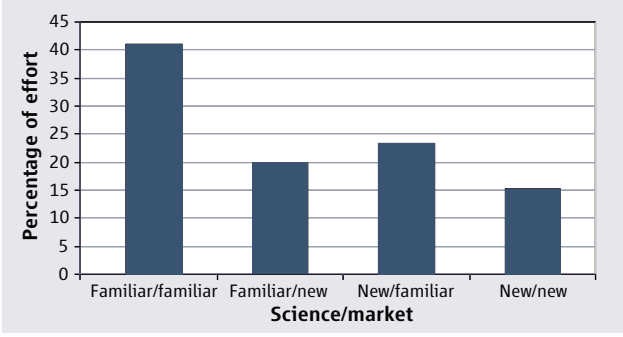
A survey shows that companies conduct most new science in developed rather than developing economies for reasons that may not always characterize the U.S. situation.

Jerry Thursby and Marie Thursby*

The idea that the United States dominates cutting edge science and technology is challenged by the decline in the U.S. share of patents and the growth of corporate spending on research and development (R&D) in emerging countries like China and India (*1*–*3*). Because scientific discovery is critical to economic growth, these trends have sparked concerns as to what is driving companies to conduct R&D in these countries and the implications for future competitiveness, particularly given problems with the U.S. patent system and improving protection of intellectual property (IP) in emerging economies (*4*–*9*). Similar concerns pervade European innovation policy initiatives (*10*). The popular press has fueled these concerns with reports of R&D moving to emerging countries in search of low costs (*11*).

A survey we conducted of 249 R&D-intensive companies headquartered primarily in the United States and Western Europe revealed that respondents expect their R&D to grow in emerging economies and to decline in developed economies for complex reasons (*12*, *13*). Lower R&D cost in emerging economies was not the main reason; market factors, collaboration with university scientists, and quality of R&D personnel were all at least as important as cost (*12, 14*).

Here we focus on the type of R&D conducted in different countries and argue that appropriate policies in the face of globalization should focus not only on the factors affecting location but also on the type of R&D conducted. We categorize R&D according to a taxonomy suggested by R&D executives as one they use in tracking internal R&D. This allows us to focus on the extent to which companies use cutting-edge science and show that the type of industrial R&D differs substantially in developed versus emerging country sites. An econometric model is used to relate the type of R&D at various sites to country characteristics. In the survey, respondents were asked to identify a recently established or currently planned R&D facility both outside and inside the home country. Respondents identified 145 facilities in developed economies (primarily the United States and Western Europe) and 90 in emerging economies (primarily China and India). They were asked to characterize the technological and market focus of R&D at the site. The technological focus was defined as either (i) a novel application of science as an output of the R&D (it could be patentable or not) or (ii) an application of science currently used by the firm and/or its competitors. We refer to (i) as new science and (ii) as familiar science. The market focus was defined as either (iii) to create products or services that are new to the firm or (iv) for the improvement of products or services that the firm already offers its customers or where it has a good understanding of the end use. We refer to (iii) as new markets and (iv) as familiar markets. Combining these foci gives four types of R&D: new science to create new markets, new science to improve familiar markets, familiar science to create new markets, and familiar science to improve familiar markets.



Type and purpose of R&D.

To clarify, when Pfizer developed Viagra, it was a new molecular structure with application in a market not served by Pfizer. It was new science for a new market. Cialis, based on the same molecular structure, was later developed by Lilly to serve a new market for Lilly. It was familiar science for a new market. Once-a-week versions developed by either company would be familiar science for familiar markets.

We asked respondents for the percent of effort at the site devoted to each of the four categories (see figure, above). The R&D executives we interviewed claimed this classification is more relevant to their R&D than the more "linear and sequential" taxonomy of basic or curiosity-driven research, applied research designed for specific end use, or development to improve products or processes (*15*). The two taxonomies provide different views of corporate R&D. For example, in 2004 the National Science Foundation reported that 4% of U.S. industry expenditure on R&D was for basic research, 19% was for applied research, and 77% was for development (*1*). By contrast, in our taxonomy, 38.8% of R&D at identified sites involves new science, while 61.2% is familiar science.

The focus here is on the percent of effort devoted to new science, regardless of whether it is for new or familiar markets. The histograms in the chart (p. 1548) give responses for the percent of effort devoted to new science in developed versus emerging economy sites. The percent of effort devoted to new science in developed economy sites is more evenly distributed than it is for sites in emerging economies. In the latter, almost 71% of the sites conduct 25% or less new science. On average, 49.6% of R&D effort in developed economy sites is for new science; in emerging economy sites, it is only 22%. The contrast is more striking when responses are weighted by the number of technical employees at each facility: The weighted averages for new science are 56% in developed economy sites and 11.5% in emerging economy sites.

To identify factors behind the type of science at a site, a logistic regression approach for grouped data was used to relate the ratio of new to familiar science in the identified facilities to respondent views of a variety of other country-specific characteristics (*16*). The model controls for industry, the firm's total worldwide technical employment, and whether the country of the facility is developed or emerging. Data for the other country char-

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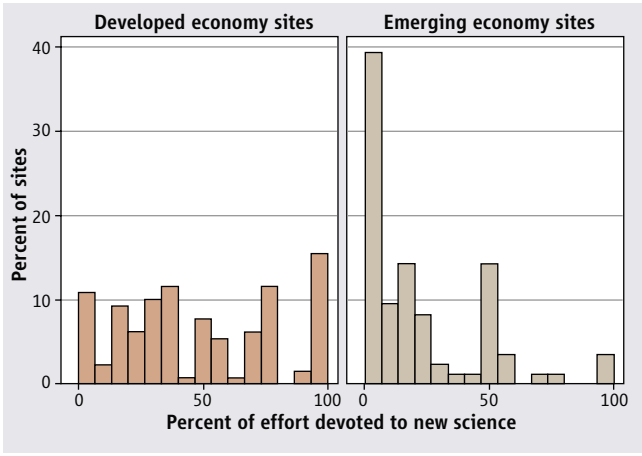
acteristics come from an index created from responses regarding a series of statements or factors that, if true for a country, would be a positive factor for locating a facility there. For each factor, respondents were first asked the extent to which they agree or disagree that the factor accurately characterizes the country in which the facility is located. They were then asked how important or central the factor was in the deliberations on location of the facility. Responses on agreement and importance were combined to create a measure of the extent to which a factor drove the location decision. We then tested the hypotheses that some of these factors are also central to the type of R&D conducted (see table below).



New science in developed and emerging economy sites.

Because one would expect the availability of high-quality personnel to be important for any kind of scientific research, it is not clear how the ratio of new to familiar science would vary (if at all) with the quality of personnel. Our regression analysis showed that, although quality of R&D personnel affects location decisions, it is not significantly related to the type of science. Cost was significantly related to the type of science with an increase in cost decreasing the ratio of new to familiar science. Growth potential and supporting sales were expected to be more important for familiar than new science, because R&D in those cases is likely to be product localization. An increase in market potential or a facility that supports sales is associated with a decreased ratio of new to familiar science. Results for the two IP factors were similar to those for quality of personnel, in that the IP factors were statistically important in location decisions, but were not significantly related to the ratio of new to familiar science. Thus IP protection appears to be equally important for both new and familiar science. In terms of the Viagra/Cialis example, it would not be surprising that Pfizer and Lilly consider IP protection equally important for both products, even though the former represents new science and the latter familiar.

The most striking result is that the factors related to universities (presence of university faculty with special expertise and ease of collaboration with universities) had the strongest impact on the type of science conducted. Each is statistically significant in the regression, and an improvement in either leads to a substantial increase in new relative to familiar science (*16*).

The relative importance of factors is summarized in the table, left (*17*). With regard to government and university policy, these results suggest that, for developed economies to maintain an advantage for cutting-edge corporate research, the keys are maintaining excellence and accessibility of research universities. The new science at sites identified by our respondents is largely conducted in developed economies, and this is significantly related to university factors. In the survey, respondents were more likely to agree that both faculty expertise and ease of collaboration with universities are greatest in developed economies.

Nonetheless, there is a cautionary message. Although respondents claim it is easier to collaborate with universities in developed countries, there is mounting evidence of changing corporate sentiment. U.S. universities have become more aggressive in negotiating IP terms, enough so as to instigate policy discussions on new guidelines for corporate-university research agreements (*18*). Recent research on university industry collaboration in the European economies that have adopted U.S. policies regarding university research shows similar concerns (*19*). This dynamic will only be accentuated as the quality of universities in emerging economies improves.

Relative Factor Importance

Factor*	Rank
University collaboration	1
Faculty expertise	2
Cost	3
Growth	3
Supporting sales	5
IP protection	Not important
Ease of ownership	Not important
Quality R&D personnel	Not important

*Costs of R&D are exclusive of tax breaks and government assistance; growth refers to market growth potential in that country, Ease of ownership is the ease of negotiation for ownership of IP from research relationships, and IP protection refers to its strength.

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20. Supported by the E. M. Kauffman Foundation and Government University Industry Research Roundtable of the National Academies.

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5805/1547/DC1

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PHYSICS

Microwave Cooling of an Artificial Atom

Quantum computers need to be isolated from environmental disturbances including the effects of thermal noise. A method has been found to cool a quantum computing element to low temperatures relative to its surroundings.

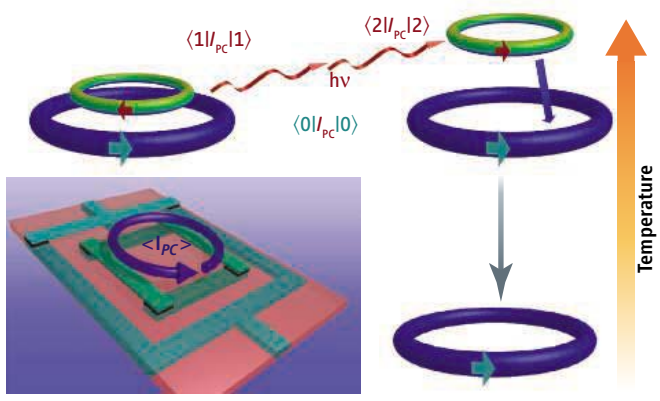
Irinel Chiorescu

Quantum computers could potentially perform difficult calculations at unparalleled speeds. Instead of being based on conventional digital bits, however, such computers would use elementary units called quantum bits, or qubits. Owing to its quantum nature, a qubit can exist in states spanning any combination of two basic wavefunctions $|0\rangle$ and $|1\rangle$, whereas classical bits have values of either 0 or 1. Consequently, an operation on one qubit causes simultaneous operations on each of the combination's components, which can be used to speed up certain kinds of calculations. Likewise, a single operation on a multiqubit system can affect a huge amount of information, compared with just changing a single bit from 0 to 1. This property is called quantum parallelism and lies at the heart of quantum information technology. Coherence, the ability to protect the quantum operations from deterioration, is the primary challenge for scientists in this field.

Quantum information is very delicate and its manipulation with laboratory electronics often proves to be a tremendous challenge. Scientists are therefore constantly working on new methods to reduce the effect of noise and to preserve the coherence of a quantum bit. On page 1589 of this issue, Valenzuela *et al*. report a method to lower the temperature of a solid-state superconducting qubit by up to two orders of magnitude relative to the temperature of the surrounding electronics (*1*).

The technique they used was originally developed for atomic systems. Atoms are among the earliest and best studied quantum entities, and their application to the quantum information field is nowadays pursued with enthusiasm. At the same time, solid-state qubits—often called artificial atoms—have great prospects of being fabricated in large numbers on electronic chips by means of conventional lithographic techniques. Solid state artificial atoms therefore combine easy fabrication with our deep knowledge of quantum atomic physics.

There are several types of superconducting qubits, one of which is the persistent current qubit or flux qubit studied by Valenzuela *et al*. It consists of a superconducting loop interrupted by three Josephson junctions (black regions between the green strips in the figure). The Josephson junctions are engineered such that the loop's energy can be described by discrete energy levels (*2, 3*)—analogous to an atomic system—contained in a two-well potential. The relative position of levels can be selected by applying an external magnetic flux through the qubit loop. The $|0\rangle$ and $|1\rangle$ states of the qubit are the lowest levels and are localized in separated wells. They are characterized by opposite directions of the persistent current I_{PC}, namely counterclockwise and clockwise, with average currents $\langle 0|I_{PC}|0\rangle$ and $\langle 1|I_{PC}|1\rangle$, respectively. A surrounding SQUID (superconducting quantum interference device) is able to identify the different flux states corresponding to different qubit states and is therefore used as a qubit readout. In the experiment of Valenzuela *et al*., the device was noise-shielded in a superconductive cavity and cooled in a cryostat to minimize thermal effects.



Cooling a qubit. At lower left, the qubit (green) is surrounded by a readout SQUID (blue) able to detect changes in the average persistent current (blue curved arrow). At equilibrium with surrounding electronics (the "bath"), the ground-state current (blue rings) is countered by a small current (in green) caused by an undesired thermal population of the qubit first excited state $|1\rangle$. Cooling of the qubit is achieved by driving the thermal population of $|1\rangle$ to $|2\rangle$ with photons (red). State $|2\rangle$ (shown as a persistent current in the same direction as the ground state one) decays quickly toward state $|0\rangle$, which leads to qubit temperatures much lower than the bath temperature.

Further cooling of the qubit is achieved by a clever manipulation of its quantum states, analogous to the method called optical sideband cooling used to slow down vibrational degrees of freedom of atoms (*4*). Consider the state $|0\rangle$ as the ground state and $|1\rangle$ as the first excited state. The method requires the use of an ancillary state (hence the term "sideband")—for instance, the second excited state $|2\rangle$ of the superconducting loop. The undesired thermal population of state $|1\rangle$ is driven into state $|2\rangle$, which is then followed by a fast decay to the ground state $|0\rangle$. By repeating the cycle a number of times, the thermal population of state $|1\rangle$, and therefore the qubit's temperature, is decreased considerably.

There is one trick, though: The $|0\rangle$ to $|1\rangle$ equilibration rate and the $|2\rangle$ to $|1\rangle$ decay rate have to be considerably smaller than the $|2\rangle$ to $|0\rangle$ relaxation rate (indicated by the blue arrow in the figure). In the case of the persistent current qubit, the applied flux bias is such that state $|1\rangle$ and states $|0\rangle$ and $|2\rangle$ are localized in different wells (with different current directions but flowing inside the same loop, as illustrated in the figure). Thus, the intrawell relaxation rate dominates the dynamics and active cooling of the qubit is possible. Here, $|0\rangle$, $|1\rangle$, and $|2\rangle$ refer to qubit states, whereas in optical sideband cooling they refer to atom states coupled with the confining trap states.

Valenzuela *et al.* achieve activation of state $|2\rangle$ by applying classical electromagnetic fields via an on-chip antenna located near the SQUID-qubit structure. With this configuration they identify three regimes. At high frequencies, several subgigahertz photons are used to resonantly activate the $|1\rangle$ to $|2\rangle$ transition (the red arrows in the figure). At intermediate frequencies, the electromagnetic field shifts the qubit levels nonadiabatically and modulates the resonant activation. At low field frequencies below 10 MHz, levels $|1\rangle$ and $|2\rangle$ exchange adiabatically their position

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and population. Optimized cooling occurs when the electromagnetic field's amplitude is such that states $|1\rangle$ and $|2\rangle$ are in resonance at full swing in their oscillatory motion.

Despite the large size of the structure—compared with the optical cooling of atoms—Valenzuela *et al*. attain a remarkably low qubit temperature of just 3 mK above absolute zero. The procedure is robust when repeated at various bath (i.e., the substrate and surrounding electronics) temperatures ranging between 30 and 400 mK. Depending on the frequency regime, the qubit effective temperature is found to range between 3 and 50 mK. The adiabatic (low-frequency) regime is particularly attractive for cooling because it results in a constant 3 mK qubit temperature, independent of bath temperature. Qubit cooling is remarkably fast, it takes only about 1 μs and the effect persists for ~300 μs at 30 mK. This equilibration time decreases drastically, however, when bath temperature is increased. As a figure of merit, the ratio of equilibration and cooling times ranges between one and several hundreds, depending on bath temperature. Such a figure of merit could give an indication of the effectiveness of the process. If it would take longer to cool the qubit than it takes to warm it back up, the process would not be efficient.

Although the microwave cooling method reported by Valenzuela *et al*. is acting on the qubit only and not on the noise sources of its surroundings, the study is an important advance for quantum computing. It provides a means to improve qubit readout, initial state preparation, and resetting of the qubit. The active cooling technique demonstrated here could be used to lower the temperature of any oscillator-like part of a chip. Moreover, the method is in principle applicable to ^{3}He refrigerators working at ~250 mK, to bring the essential parts of the chip to millikelvin temperatures. And finally, techniques developed in quantum optics could be blended with the rich physics of solid-state systems, yielding great benefits in the long run.

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10.1126/science.1136100

ASTRONOMY

A Ghostly Star Revealed in Silhouette

One class of binary stars, in which white dwarfs accrete material from low-mass companions, has long been predicted, but their dimness has made observations difficult. Evidence that they exist now comes from the Sloan Digital Sky Survey.

Pierre F. L. Maxted

If our current understanding of the evolution of binary stars is correct, the Galaxy should be littered with the remains of stars that have been reduced to about 5% of the Sun's mass ($0.05M_{\odot}$) by extensive mass loss onto their white dwarf companions. White dwarfs are the small, dense collapsed cores of deceased stars. A binary star system in which a white dwarf accretes material from a companion (see the figure) is called a cataclysmic variable (CV). Every kilogram of material that falls onto the white dwarf gains the energy equivalent of a few kilotons of TNT. Much of this energy is released as ultraviolet or x-ray radiation. Many CVs have been identified from this highly variable, short-wavelength light produced by rapid mass transfer onto the white dwarf. However, most CVs should have evolved through this violent phase to become a "dead CV" with a low-mass companion that can support only weak mass transfer. Extensive efforts to confirm this long-standing prediction have failed to identify any CVs that have clearly survived the rapid mass transfer phase of their evolution. Now, on page1578 of this issue, Littlefair *et al.* (*1*) report the unambiguous detection of a dead CV from a direct mass measurement of the low-mass companion in the CV SDSS 103533.03+055158.4 (SDSS 1035 for short). Why has it taken more than 20 years to find a dead CV, and why does it have such a dull name? The answer lies inside your digital camera.

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Digital cameras use charge-coupled devices (CCDs) to detect light. CCDs have revolutionized astronomy because they detect up to 90% of the light falling on them, versus a few percent at best for photographic film. Large-format CCDs are now relatively inexpensive, so it has become possible to build instruments that use arrays of CCDs to survey large areas of the sky. The Sloan Digital Sky Survey (SDSS) is the most ambitious sky survey undertaken to date. Researchers in the SDSS consortium have used a 120-megapixel camera to measure the brightness of more than 200 million celestial objects over a quarter of the sky at five wavelengths. Interesting objects are then followed up by means of spectrographs fed by optical fibers that can observe hundreds of objects simultaneously. The first phase of the SDSS obtained spectra for almost 1 million objects, including more than 150 new CVs. It is clearly not possible to make up interesting names for all 200 million stars and galaxies, so each object is named after its position on the sky.

The CVs identified by the SDSS are typically fainter by a factor of 100,000 than stars visible to the naked eye—much fainter than most known CVs (*2*). This is only partly due to their being, on average, farther away than known CVs; they are also intrinsically less luminous than known CVs (i.e., they have low mass-transfer rates). The sample of CVs selected from the SDSS is also much less affected by sampling bias than existing samples, so it is a good place to search for a missing population of dead CVs. The challenge is to find a technique that can reliably measure the mass of an almost invisible companion to a very faint star. Littlefair *et al.* have used CCDs, a large telescope, and a bit of luck to meet this challenge.

A typical CV is smaller than the Sun, so there is a good chance that the orientation of the binary is such that the companion eclipses the white dwarf once every orbit as seen from Earth. This will lead to an apparent dimming of the CV every orbit during the few minutes that the companion blocks the light from the white dwarf. SDSS 1035 is an eclipsing CV, so there is a wealth of information to be gleaned from the changes in brightness during the eclipse. These show, for example, that the mass transferred from the low-mass companion forms a disc around the white dwarf with a bright spot on its outer edge due to the inflowing material. The geometry of the binary can be determined by measuring the times at which different

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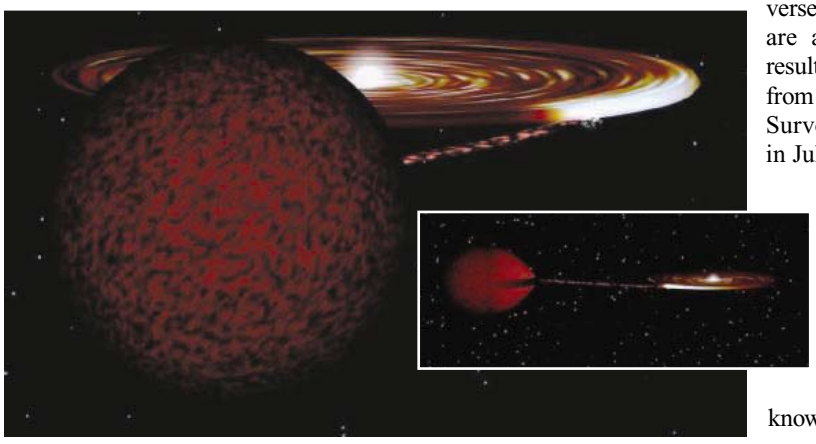
sources of light are eclipsed. The orbital period of SDSS 1035 is only 82 min, so small features such as the white dwarf are eclipsed in less than a minute.

To accurately measure these rapid changes in brightness in such a faint star, Littlefair *et al.* used a telescope with an aperture of 4.2 m and ULTRACAM, an instrument they designed that uses CCDs to measure the brightness of CVs and other rapidly varying stars. The data quality is impressive and leads to a mass for the companion accurate to about 4%. This is good enough to show convincingly that they are observing a genuine dead CV because the companion is well below the limit of $0.072 M_{\odot}$ below which a star cannot sustain nuclear reactions in its core. Objects that are born with masses below this limit are known as brown dwarfs. It remains to be seen whether this nomenclature will also be adopted for companions to dead CVs. Whatever they are called, it is the change in structure of the companion near this limit that causes the mass transfer rate to decline and the CV to fade from view.



Binary transfusion. A simulation of the accreting binary SDSS 103533.03+055158.4 based on the parameters measured by Littlefair *et al*. The binary is pictured at the orbital phase just before the eclipse of the bright white dwarf star by the larger and much fainter low-mass companion star. Also visible is the bright region caused by the impact of the stream of material from the cool companion onto the accretion disc. **(Inset)** SDSS 1035 viewed at an orbital phase where the stars are seen side-on.

Does the Galaxy contain other dead CVs like SDSS 1035? The SDSS continues to be a gold mine for finding examples of rare types of CV and other fascinating objects in the universe. Other large-scale surveys are also starting to produce results: The first release of data from the UK Infrared Deep Sky Survey (UKIDSS) took place in July this year (*3*), the Galaxy Evolution Explorer satellite (GALEX) is constructing a new map of the ultraviolet sky (*4*), and there are several even more ambitious surveys coming online over the next few years. Who knows what treasures are hiding among the billions of stars, galaxies, and quasars that will be observed from ultraviolet to infrared wavelengths? We can certainly expect to hear more about fascinating stars with uninteresting names.

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ASTRONOMY

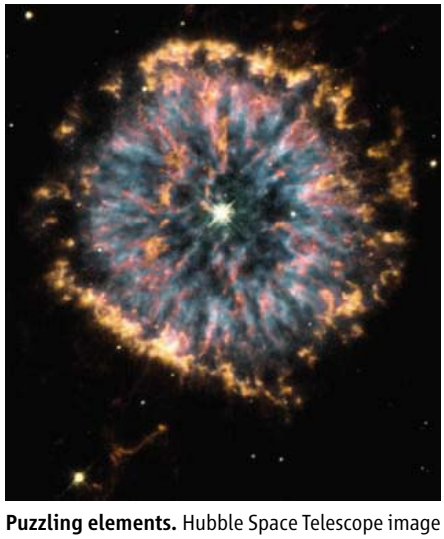
Big Bang Points to Stellar Mix-Up

Computer models of evolving stars show the discrepancy between the amount of helium-3 predicted and the amount actually observed in the universe.

Philipp Podsiadlowski and Stephen Justham

One of the major successes of the Big Bang model is the prediction of light-element production, but some troubling inconsistencies have lingered. One of these has been known as the "^{3}He problem." Although the predicted abundance of the helium isotope ^{3}He is consistent with its abundance measured in the interstellar medium (ISM), stellar evolution theory has long predicted that low-mass stars (i.e., stars not much more massive than the Sun) are copious producers of this isotope, and so we should observe much more of it than we actually do. On page 1580 of this issue, Eggleton *et al.* (*1*) report a resolution to this cosmological puzzle in which they convincingly identify the mechanism by which low-mass stars avoid the overproduction of ^{3}He.

Deuterium, one of the other light elements produced in the Big Bang, is always destroyed inside stars by conversion into ^{3}He, but ^{3}He itself can be both destroyed and produced. Standard models of low-mass stars predict that outside the stellar core, the abundance of ^{3}He is increased by one to two orders of magnitude over the primordial ^{3}He abundance. In the final stage of evolution, when the star ejects its outermost layer to form a planetary nebula (see the figure), this newly produced ^{3}He should be ejected into the ISM, causing a gradual increase in the abundance of this isotope with time. Such ^{3}He overabundances have been observed in some planetary nebulae (*2*), yet there is no evidence for a systematic gradual increase of the ^{3}He abundance in the ISM. Apparently, most low-mass stars do not produce and eject large amounts of this isotope. It has long been suspected that this requires an additional mechanism that mixes material from the envelope deeper into the star, where the temperatures are high enough for ^{3}He to be destroyed. Most previous sug-



Puzzling elements. Hubble Space Telescope image of the planetary nebula NGC 6751. Planetary nebulae are produced in the final stage of a low-mass star, where a star ejects its envelope and enriches the interstellar medium with elements produced in its previous evolution.

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gestions have invoked mixing due to rotational effects. However, we know from seismological measurements of the Sun that its core is essentially in solid-body rotation. This precludes rotational mixing as an important process at some distant time in the future when the Sun evolves into a giant star.

The elegant new insight provided by Eggleton *et al.* is that the distribution of ^{3}He itself plays a key role in driving this additional mixing by establishing a distribution of ^{3}He in the star that is susceptible to a Rayleigh-Taylor instability. This is similar to the well-known instability in everyday life where a dense fluid on top of a lighter fluid leads to the mixing of the two fluids. Even though the unstable gradient produced by ^{3}He is tiny, the authors demonstrate, using three-dimensional, hydrodynamic stellar calculations, that this leads to rapid mixing and the destruction of ^{3}He.

These calculations are some of the first results of an ambitious project led by Eggleton and Dearborn at the Lawrence Livermore National Laboratory (LLNL) to realistically model stars in three dimensions using a computer code named "Djehuty." The important difference between Djehuty and all other stellar evolution codes is the inclusion of three-dimensional hydrodynamics, which can account self-consistently for mixing and nonspherical effects. This is a step requiring a great deal of effort in both code development and computational brute force.

These results highlight the importance of improving the underlying physics in stellar models, especially because the driving physics in this particular case would be easy to ignore; this apparently minor consideration can be seen to have very important results.

Djehuty is still a work in progress: Impressive though their work already is, to model binary stars they will require an aspherical gravitational potential and will need to increase the number of hydrodynamic mesh points they use in the simulation by four orders of magnitude (*3*). Even the addition of rotation will cross another interesting threshold.

Stars cannot yet be genuinely evolved through their lifetimes with Djehuty, even with the computing resources at LLNL; in fact, the calculations presented by Eggleton *et al.* contain less than a day's worth of stellar evolution. To put this in perspective, for Eggleton's one-dimensional stellar evolution code, "an evolutionary sequence requires about 60 min from the main sequence to the helium flash"—and that was in 1971 (*4*). It will be a very long time before three-dimensional stellar evolution calculations can be done as rapidly and routinely as today's one-dimensional codes.

The example of the ^{3}He problem and its resolution illustrates that, to understand the origin and evolution of the universe, we need to understand stars, and vice versa. In particular, the predictions of Big Bang nucleosynthesis have pointed to a problem in stellar modeling. On the other hand, there are many examples where an understanding of stars in the local universe would lead to a better understanding of the evolution of the universe and its constituents on the large scale. Besides the ^{3}He problem, there is also a ^{7}Li problem. The Big Bang prediction of the ^{7}Li is at least a factor of 2 higher than is observed in metal-poor stars (*5*), and in this case extra mixing cannot provide a simple explanation. Undoubtedly, the resolution of this puzzle will provide new insights into the physics of stars, the Big Bang, or even both.

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CHEMISTRY

Pulling Strings

A toolkit of DNA-based devices can be used for computational circuits.

Walter Fontana

Computing devices, like the information they process, are embodied in a material substrate constrained by the laws of physics (*1*). The design of modern computing devices has nevertheless succeeded to a remarkable extent in separating hardware from software and questions specific to physics from questions specific to computation. In such a setting, abstract formalisms of the kind envisioned by Turing (*2*) can justifiably ignore the nature of materials and issues such as energy dissipation and material stability.

However, this separation between hardware and software—and hence physics and computation—breaks down when device features approach atomic scales or when the devices that process information are of the same class as the information itself. How, then, can we realize computation in the world of molecules and their chemical reactions? On page 1585 of this issue, Seelig *et al.* (*3*) provide an answer to this question.

One way to formally express computation is in terms of rules that rewrite words. Molecules, like words, are combinatorial structures, and chemical reactions can provide the required rules, if we can program chemistry. To exert the necessary control over chemistry, we must be able to specify which components in a mixture of molecules interact when, and where. This control can be achieved by designing appropriate single-stranded DNA (or RNA) sequences that bind to each other like Velcro's hook and loop fasteners, but in an addressable manner. Based on this idea, Seelig *et al.* exploit a simple principle—strand displacement—to implement not just logic gates, but also a toolkit of devices for building molecular circuits of a digital kind.

In the past decade, DNA (or RNA) sequences have been used to find solutions to combinatorial problems by self-assembly (*4*), to encode complete decision trees for simple games like tic-tac-toe (*5*), and to build programmable sensors of cellular states (*6*). DNA has also been used to build nanostructures and nanomechanical devices (*7, 8*), as well as two-dimensional grids that can function as frames of reference for placing such devices at specific locations (*9*). For example, Seeman and co-workers (*10*) have developed a rotary device that consists of two DNA strands woven into two pairs of helices, with a flexible hinge region in between. This device can act as a programmable, molecular-scale robot arm. On page 1583 of this issue, Ding and Seeman (*11*) report the deliberate, function-preserving placement of such a device in a two-dimensional array of DNA tiles.

There are two reasons for the versatility of

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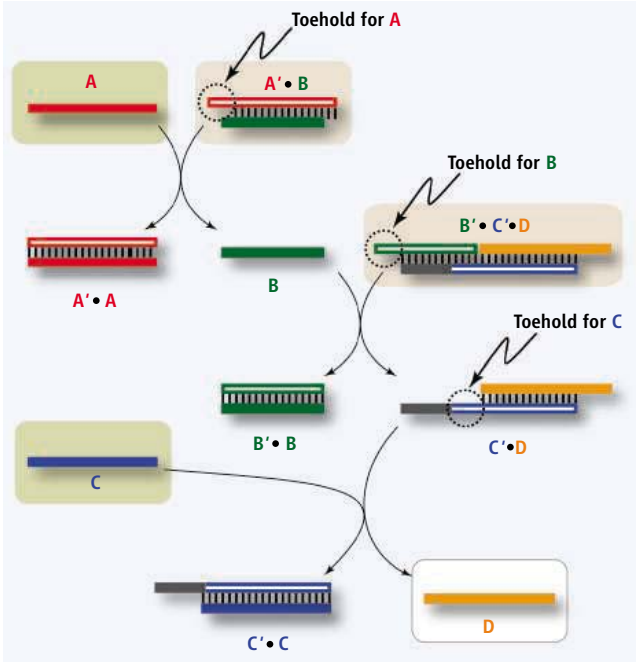
DNA as a structural, mechanical, and computational substrate. First, the Watson-Crick base-pairing rules provide a natural foundation for programming the interaction specificity of DNA sequences. Second, base pairing provides the free energy needed to deliberately change structures and move computation forward. A DNA strand will let go of its binding partner if a third strand offers base pairs that are energetically more favorable. A DNA sequence thus serves both as a specific instruction and as the fuel needed for its own execution.

To illustrate the case of Seelig *et al.*, consider two sequences A′ and B that form a complex A′B by virtue of complementary segments. In the presence of a strand A that offers more favorable base pairs to A′ than B, a displacement reaction A + A′B → AA′ + B will occur (see the figure). The DNA complex A′B therefore stands for the statement "if A then B′, because it yields B when it encounters A. In this scheme, the gate "B AND C" translates into a statement like "if (B and C) then D", which is a DNA complex designed to release strand D as a result of two sequential displacement reactions that require the presence of B and C (see the figure).



Gate composition. The translator gate A′B (gray box in top row) exchanges strand A for B. B then triggers the "B AND C" gate (B′C′D, gray box in second row). Together, the two gates form an "A AND C" gate that emits a D-strand in the presence of inputs A and C (light green boxes). Open and filled bars represent complementary sequence segments. If D were A (or give rise to A, as accomplished by a translator D′A), the end product could reenter the cascade at the top, creating a feedback loop.

In such a system, logic gates are molecular (DNA) complexes that execute their logic through reactions. Gates constructed in this way can be concatenated, because the output string released by one gate can react with another gate in the mixture, much like in biological signaling cascades. For example, an "A AND C" gate can be implemented by using a "B AND C" gate in conjunction with an "if A then B" construct that exchanges A for B (see the figure). This is analogous to address forwarding in a Web browser.

A test tube typically contains many copies of a given gate complex that undergo displacement reactions in accordance with the binding preferences programmed into their DNA sequences. Because these reactions yield a noisy output-strand concentration, digitization of the output yield as "high" (true) or "low" (false) is required to interpret a DNA gate as a logic operation.

Seelig *et al.* provide a toolkit of DNA-based reactions for such digital signal processing. The tools include thresholds to remove leaks and amplifiers to restore signal strength. For example, an amplifier permits one input strand to cause the release of more than one output strand copy. This can be achieved by a feedback construct involving two gates that mutually trigger each other ("if A then B + if B then A") as soon as input strand A appears in the mixture. Alternatively, the input strand has been used as a catalyst for refolding a metastable DNA complex in a process that also releases an output strand (*12*). In this way, the same input strand can help to refold several complexes, leading to output amplification.

It can be difficult to design sequences that make up large circuits. Complementary regions in a DNA sequence can cause a strand to fold back upon itself, potentially blocking further computation. Accidental complementarities across sequences can lead to interference between computations, in analogy to cross-talk in biological signaling systems. Seelig *et al.* use a computational optimization procedure to design sequences that minimize the likelihood of such complications. They validate their architecture and design tools with a dazzling circuit of 11 gates and six inputs.

What might this prototype technology be good for? The authors envision analytical applications in systems biology, such as the in situ detection, quantification, or amplification of microRNAs and transcription patterns. But this scalable molecular programming language may also provide a means for choreographing the assembly and operation of future nanometer-scale devices.

Unlike electronic circuit elements, DNA gates and their inputs are used up as the computation unfolds through chemical reactions; hardware and software are one and the same. Yet, what appear to be limitations may turn out to be intriguing opportunities. As gates are transformed by the very computations they control, can new gates assemble as by-products? Could one devise a computational gate "metabolism" that maintains an ensemble of gates through a catalytic cycle?

Milner has devised a calculus (*13*) that views every component of a distributed computational system as an interactive process, whose channels are consumed upon communication. Seelig *et al.* may unknowingly have come close to implementing design aspects of that calculus in chemistry. Theoretical computer scientists may find inspiration in a chemical model of an influential abstraction. In return, modifications of this calculus may become useful in the design and analysis of DNA gate systems.

Over the past half-century, the idea has taken hold that physical processes, particularly in biological systems, can be understood as computation. A back-and-forth between transparent experimental models of molecular computation and the development of formal tools for reasoning about concurrent behavior might lead to a better appreciation of what it means for cells to "compute," "organize," or "process information" and, perhaps, evolve.

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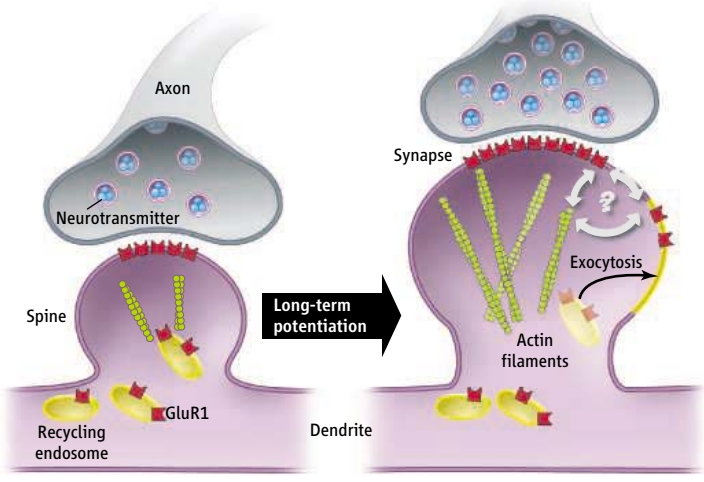
NEUROSCIENCE

Matters of Size

Charles Kopec and Roberto Malinow

Bigger dendritic spines are associated with stronger neural connections. Now underlying mechanisms for this association are being revealed.

From the overall body plan of an organism to the intricate three-dimensional fold of proteins, structure is a key determinant of function. Neurons, the fundamental cells of the nervous system, are no exception. The architecture of their dendritic and axonal arbors—the cellular extensions that receive and transmit information—determines which neurons they can connect to, whereas the diameter of these extensions determines the speed and filtering of electrical signals that travel down them. Tiny femtoliter (10^{-15} liter)–sized protrusions from neuronal dendrites, called spines, receive a functional connection from another neuron's axon at a specialized area of contact known as a synapse. A study by Park *et al.* in a recent issue of *Neuron* (*1*) marks a large step forward in our understanding of how spine size and synaptic strength are balanced.



Balancing act. Long-term potentiation drives exocytosis of recycling endosomes, providing dendritic spines with more membrane and receptors (GluR1). Actin polymerization provides structural support. These processes are somehow balanced to regulate the size of spines and the strength of synaptic connections.

A neuron can have up to 100,000 spines, each generally forming a single synapse. Spines function as chemical compartments for signaling molecules that become activated by specific patterns of synaptic transmission (*2*–*4*). This organization provides each synapse with a miniature caldron in which to concoct a chemical brew to effect changes in connections between neurons (*5*).

Interestingly, large spines contain strong synapses (robust transmission) and small spines have weak synapses (*6*, *7*). A spine is at least an order of magnitude larger than a synapse, and thus there is no physical requirement for this correlation. The reason for this correlation between structure and function remains elusive, but an abundance of circumstantial evidence points to its importance. Stimuli that cause stable changes in synaptic strength lead to corresponding stable changes in spine volume (*8*, *9*). Heritable forms of mental retardation can present abnormalities in spine morphology as well as synaptic function (*10*). Furthermore, Alzheimer's disease may involve a loss of spines that is fundamentally linked to a decrease in the number of neurotransmitter receptors at the synapse (*11*). Therefore, understanding how and why this correlation between synapse strength and spine size exists will not only expand our understanding of how synapses work, but may have clinical relevance as well.

Park *et al*. elegantly combine serial section electron microscopy and live cell fluorescence microscopy to afford us a view of the inner workings of spines. The authors stimulated cultured mammalian neurons to generate a stable increase in synaptic strength known as long-term potentiation (LTP), and confirmed that the rapid increase in synaptic strength is accompanied by a matched increase in spine volume. They then probed the molecular and cellular mechanisms behind this correlation.

Park *et al*. focused on the role of the recycling endosome, an intracellular membrane-bound compartment that is part of the system that transports membrane-bound proteins onto and off the cell surface. Previous work by this group showed that the protein GluR1 is delivered to the neuronal surface from the recycling endosome through exocytosis, the cell's secretory process (*12*). GluR1 is a glutamate receptor subunit that is inserted into synapses during LTP and plays an important role in mediating the increase in synaptic strength (*13*). Blocking this delivery by expressing mutant proteins that specifically inhibit this exocytosis prevented the stable increase in synaptic strength.

In the present work, Park *et al*. provide tantalizing evidence that the lipids delivered to the neuron's surface from the vesicles carrying GluR1 are the raw materials that allow the spine to enlarge (see the figure). The recycling endosome appears to be situated in the right place, just below or even within some spines, and is of sufficient size to influence spine volume. LTP-inducing stimuli mobilize these endosomes from dendrites into spines, positioning the endosome perfectly to fuse with the spine surface. Blocking exocytosis from this compartment prevents spines from enlarging, strongly suggesting that the recycling endosome is a source of structural plasticity. Furthermore, the amount of surface area lost in the endosomal system equals the amount gained by the spines, hinting at a direct transfer of material. Park *et al.* also directly visualize exocytosis with a pH-sensitive fluorescence indicator that translates the pH change experienced during exocytosis (the pH inside the recycling endosome is acidic, whereas in the extracellular space it is mildly alkaline) into a large change in fluorescence. By monitoring events simultaneously, these experiments reveal that exocytosis takes place directly in spines and that the amount of exocytosis correlates extremely well with the increase in spine volume.

Although this study elucidates how spine size and synaptic strength are kept in check, it is not the whole story. Several groups have investigated the role of the actin cytoskeleton in determining spine morphology (*14*, *15*). Indeed, LTP causes an increase in the amount of filamentous actin in spines (*16*, *17*), and preventing the formation of filamentous actin blocks structural (*16*) and functional (*18*, *19*) changes during LTP. It is difficult to imagine how lipids that are added to the spine membrane could be sufficient to make a larger spine, rather than simply flow off into the membrane of the dendrite. It is thus likely a combination of actin polymerization and the exocytosis of recycling endosomes that mediate spine enlargement during LTP. Filamentous actin acts as a skeleton to support a larger spine, whereas more lipids are the raw material to increase the spine's surface area.

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But if these two processes are required for structural and functional plasticity, how are they balanced? That is, how are the distinct molecular cascades underlying exocytosis and actin cytoskeletal reorganization coordinated? Perhaps evolution has perfectly balanced their rates, or maybe there is a physical link between the two systems. For instance, receptors delivered to the synapse from the recycling endosomes could stabilize the actin cytoskeleton and thereby provide a simple accounting process to balance changes in synaptic strength and spine size. Maybe when we fully understand how spine size and synapse strength are coordinated will we be poised to comprehend why spine size matters.

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EVOLUTION

The Puzzle of Human Sociality

Human cooperation may have evolved as a consequence of genetic relatedness, culture, or language within groups.

Robert Boyd

The scale and complexity of human societies present an important evolutionary puzzle. In every human society, people cooperate with many unrelated individuals. Division of labor, trade, and large-scale conflict are common. The sick, hungry, and disabled are cared for, and social life is regulated by commonly held moral systems that are enforced, albeit imperfectly, by third-party sanctions. In contrast, in other primate species, cooperation is limited to relatives and small groups of reciprocators. There is little division of labor or trade, and no large-scale conflict. No one cares for the sick, or feeds the hungry or disabled. The strong take from the weak without fear of sanctions by third parties. On page 1569 of this issue, Bowles (*1*) provides one explanation for the commonness of costly, prosocial behavior in human societies.

The behavior of other primates is easy to understand. Natural selection only favors individually costly, prosocial behavior when the beneficiaries of the behavior are disproportionately likely to share the genes that are associated with the behavior. Selection can favor altruism toward close relatives because recent common descent provides a cue of genetic similarity. The small size of primate families limits the size and complexity of the groups that can be formed through this process. Thus, standard evolutionary theory provides a perfectly good explanation for the behavior of other primates, but not humans.

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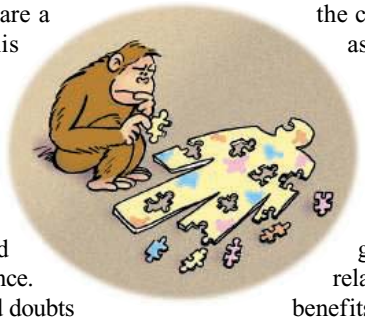
Bowles proposes that competition between genetically differentiated groups led to the evolution of our prosocial psychology. Limited migration between groups can lead to the buildup of genetic relatedness (which measures how much the possession of a particular gene in one individual predicts the presence of the same gene in a second individual) among group members. This means that group membership can also be a cue that allows assortative interaction—genes that cause you to help members of your group can be favored because other group members are disproportionately likely to carry the same genes, even though you do not share a recent common ancestor. This is an old idea. A version appears in *The Descent of Man* (*2*) and has reappeared many times since then. It has never gained much traction, however, because there have been good reasons to doubt its importance. First, theoretical work raised doubts about levels of genetic relatedness being high enough to favor prosocial behavior toward group members (*3*). Second, limited migration generates more competition within groups than between groups. This means that helping others in your own group reduces your own relative fitness and the fitness of your descendants. In some plausible models of the evolution of altruism when migration is limited, this effect exactly balances increases in relatedness, eliminating selection for altruism toward group members (*4*). Finally, the benefits of success in intergroup competition seems too small and the costs too large to allow cooperation to evolve. After all, other primates live in similar groups, but show little evidence of group-level cooperation.



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Bowles meets these objections with a combination of data and theory. First, he has assembled data on the amount of genetic differentiation among human hunter-gatherer groups (or put another way, the level of relatedness within such groups). These data show that the level of relatedness within such groups is substantially higher than previously supposed, a bit below that of cousins. This means that the cooperation will be favored as long as the benefits to individuals are about 10 times the cost. Second, because competition occurs between groups and successful groups are able to colonize the territories of extinct groups, competition among relatives does not attenuate the benefits derived from cooperation. Third, intergroup competition is common in small-scale societies, so the benefits derived from collective efforts to compete with other groups are plausibly substantial. Finally, Bowles notes that human foraging groups typically have culturally transmitted norms and practices, including food sharing and socially imposed monogamy, which reduce fitness differences within groups. He makes the original and interesting argument that such "leveling mechanisms" act like redistributive taxes to reduce the disadvantage of engaging in costly

prosocial behavior. The absence of these kinds of leveling mechanisms in primate groups may explain why human societies differ from those of other primates.

Make no mistake. This is not a "group selection" hypothesis that competes with "kin selection" hypotheses [see the Review by Nowak (*5*) on page 1560 of this issue for a discussion of conditions that favor the evolution of cooperative behavior]. Both concepts are equivalent frameworks for describing the same evolutionary process. The group (also known as multilevel) selection approach describes all natural selection as going on in a series of nested levels: among genes within an individual, among individuals within a group, and among groups. The kin selection approach accounts all fitness effects back to the individual gene. Bowles adopts the multilevel selection framework, but you can pose exactly the same argument in a kin selection framework and if you do your sums properly, you will get exactly the same answer. The real questions are: Are amounts of genetic variation observed among contemporary human foraging groups representative of the Pleistocene hominin populations in which distinctively human behavior probably evolved? Were the benefits of success (survival) from intergroup competition in ancestral human populations large enough to compensate for the individual costs of participating in such contests? And, do the kinds of leveling mechanisms observed among contemporary foragers exist and work in the same way in ancestral populations?

The role of leveling mechanisms is especially tricky. In other primate species, access to resources is usually regulated by social dominance. Dominant males monopolize mating and dominant females get better access to food, sleeping sites, and so on. There is little dominance among human foragers, and access to resources is more egalitarian. Thus, it seems likely that the variance in reproductive success in human foraging groups is lower than in other primates. However, at least some of the leveling mechanisms that we see in human groups seem to require a degree of prosociality not seen in other primates. Food sharing and dispute resolution, for example, could rest on exactly the same prosocial impulses that Bowles seeks to explain. It is certainly fair to invoke reproductive leveling to explain the stability of extended altruism among humans, but whether it is sufficient to explain its origin is not yet clear.

The main competing explanations for the distinctive level of human cooperation do not suffer from this potential liability. Some authors have argued that theory of mind, spoken language, and other cognitive innovations have allowed humans to build larger coalitions among nonkin than other primates (*6*). Others have proposed that rapid cultural adaptation generated cultural variation among groups, and intergroup competition subsequently favored the spread of culturally transmitted group-beneficial beliefs and practices (*7*). In both cases, the triggering factor (such as language or social learning) is supposed to have evolved for some other reason; cooperation and prosocial preferences arose as a side effect. Of course, there is no reason why these hypotheses need be mutually exclusive. Language or culture may have led to the evolution of leveling mechanisms, which then potentiated the spread of prosocial genes because these mechanisms reduced the costs of cooperation.

Research into evolutionary processes that spawned our uniquely cooperative societies may help us understand the nature of our social preferences. Bowles's hypothesis is consistent with suggestions that people have innate, prosocial motivations, and that these feelings are elicited by cues of common group membership. Other hypotheses seem to fit more easily with alternative views of human nature. These are old questions, but still important ones. The kind of quantitative empirical work that Bowles has done will help answer them.

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ATMOSPHERE

An Ancient Carbon Mystery

Mark Pagani, Ken Caldeira, David Archer, James C. Zachos

Sudden global warming 55 million years ago provides evidence for high climate sensitivity to atmospheric CO_2, but the source of the carbon remains enigmatic.

About 55 million years ago, Earth experienced a period of global warming that lasted ~170,000 years (*1*). This climate event—the Paleocene-Eocene Thermal Maximum (PETM)—may be the best ancient analog for future increases in atmospheric CO_2. But how well do we understand this event?

Temperature records from the tropics to the poles indicate that at the start of the PETM, global temperatures increased by at least 5°C in less than 10,000 years (*2*). The rise in surface temperature was associated with changes in the global hydrological cycle (*3*) and a large decrease in the $^{13}C/^{12}C$ ratio of marine (*4*) and terrestrial carbonates (*5*) and of organic carbon (*3*). This carbon isotopic excursion indicates that changes in the global carbon cycle were linked to global warming.

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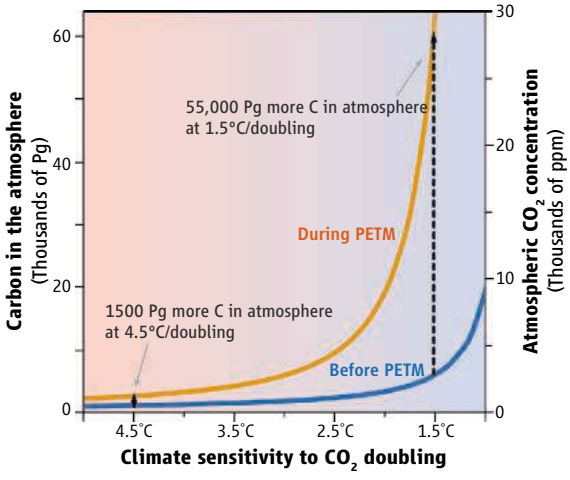
Furthermore, the ocean's carbonate compensation depth—the depth above which carbonate accumulates on the sea floor— rose substantially at the start of the carbon isotope excursion (*5*). This change is consistent with ocean acidification associated with a rapid influx of CO_2. Although the change in ocean chemistry was not uniform throughout the ocean (*6*, *7*), the confluence of isotopic and sedimentological data supports the conclusion that atmospheric CO_2 was the primary greenhouse gas driving the PETM. Yet, the source of the CO_2 remains a mystery.

Biological responses to global warming during the PETM include changes in the ecology of marine organisms, a mass extinction of benthic foraminifera (*4*, *8*), and a global expansion of subtropical dinoflagellates at the earliest onset of the event (*9*). Global warming also coincides with the appearance of modern orders of mammals (including primates), a transient dwarfing of mammalian species, and a migration of large mammals from Asia to North America (*8*).

According to one hypothesis, the PETM was caused by the release of ~2000 PgC from the destabilization of methane hydrates (which would subsequently oxidize to form CO_2) (*10*). However, it is unlikely that meth-



CO_2 input during the PETM. The amount of additional atmospheric CO_2 responsible for the PETM warming depends on the pre-PETM atmospheric CO_2 concentration and the climate sensitivity to CO_2 doubling. To determine pre-PETM atmospheric CO_2 concentrations (blue line), we assumed pre-PETM global mean annual temperature 5°C warmer than during recent pre-industrial times, when atmospheric CO_2 concentrations were 280 ppm. To determine PETM atmospheric CO_2 concentrations (orange line), we assumed a 5°C warming during the PETM and a surface ocean 5× saturated with respect to calcite.

ane was the sole source of warming. For example, the size of the methane hydrate reservoir at the end of the Paleocene was probably much smaller than it is today (*11*), and the magnitude of the sustained warming and the change in the carbonate compensation depth are compatible with a much greater mass of carbon than originally estimated (*6*). To account for larger carbon inputs, other sources have been invoked, including the oxidation of terrestrial (*12*) and marine (*13*) organic carbon and/or volcanic outgassing and thermal decomposition of organic matter (*14*). There is no single satisfactory explanation.

But whatever the source, the carbon input responsible for the PETM must have been massive. Given a global temperature sensitivity range of 1.5 to 4.5°C per doubling of the atmospheric CO_2 concentration and global mean annual temperatures perhaps 5°C warmer than during recent pre-industrial times, estimates for pre-PETM atmospheric CO_2 concentrations range from 600 to 2800 parts per million (ppm), broadly consistent with estimates from proxy data (*15*). Starting from these conditions, an increase of 750 to 26,000 ppm of atmospheric CO_2 would be required to account for an additional 5°C rise in global temperature, which implies an addition of 1500 to 55,000 PgC to the atmosphere alone (see the first figure).

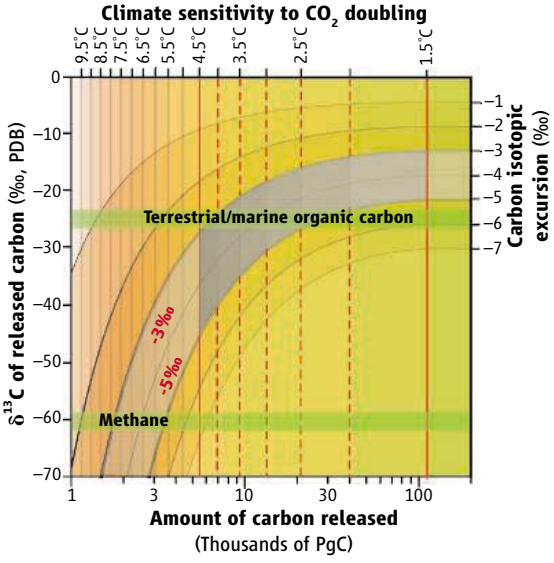
Sustaining this concentration for tens of thousands of years implies partial equilibration with the carbonate system in the ocean, indicating a total release of 5400 to 112,000 PgC (see the second figure), with 3900 to 57,000 PgC of released carbon residing in the ocean (and with additional carbon supplied by the dissolution of carbonates). The extraordinary magnitude of these estimates is evident when compared against the 5000 PgC estimated for conventional fossil fuel resources available today.

The input of carbon responsible for the PETM altered the stable carbon isotopic composition of the Eocene oceans and atmosphere. Marine carbonate records indicate a carbon isotope excursion between –2.5 and –3 per mil (‰), but records from ancient soil carbonates and plant organic matter reveal a much larger change of over –5‰ (*3*, *5*). Explanations have been presented to account for these isotopic differences (*5*), but this evidence can also suggest that the global carbon isotope excursion was larger than determined from marine carbonates (*3*).

These details may appear esoteric, but to determine the mass and source of carbon responsible for the >5°C warming during the PETM, we must match the magnitude of the carbon isotope excursion with the mean global temperature sensitivity to CO_2 and associated climate feedbacks (see the figures). One conclusion from this approach is that CO_2 derived from methane hydrates could only have caused the PETM if the climate sensitivity to CO_2 was much higher than currently assumed. Yet carbon sources other than methane, such as the oxidation of primary terrestrial and/or marine organic carbon, together with commonly accepted estimates of climate sensitivity, would require extremely large carbon inputs to explain the warming. Thus, the PETM either resulted from an enormous input of CO_2 that currently defies a mechanistic explanation, or climate sensitivity to CO_2 was extremely high.

The next challenges are to constrain the magnitude and rate of carbon input (and that of other greenhouse gases) and to develop realistic models for the cause of this anomalous, but clearly CO_2-induced global warming event. Solving this mystery will allow us to determine whether the PETM is a true analog for future climate change.

Carbon release during the PETM. The amount of carbon needed to explain a 5°C change in global mean temperature depends on pre-PETM CO_2 conditions (see the first figure) and the climate sensitivity to CO_2 doubling (including associated system feedbacks). The source of carbon released (and climate sensitivity) can be estimated from the carbon isotopic composition of the released carbon and the $\delta^{13}C$ excursion it produced. For example, assuming a carbon isotope excursion of –3 to –5‰, carbon from methane (with an average $\delta^{13}C$ value of –60‰, green bar) would imply a carbon input of 1800 to 3500 PgC and a climate sensitivity of 6.8 to 7.8°C per CO_2 doubling. Terrestrial/marine organic carbon refers to organic carbon derived from the primary production of terrestrial and/or marine plants.



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GE PRIZE-WINNING ESSAY

The Emergence of Cells During the Origin of Life

In simple protocells, formed by encapsulating RNA inside vesicles, interactions between the RNA and the membrane lead to the emergence of essential cellular behaviors.

Irene A. Chen

GE Healthcare and *Science* are pleased to present the prize-winning essay by Irene A. Chen, a regional winner for North America who is the Grand Prize winner of the GE & *Science* Prize for Young Life Scientists.

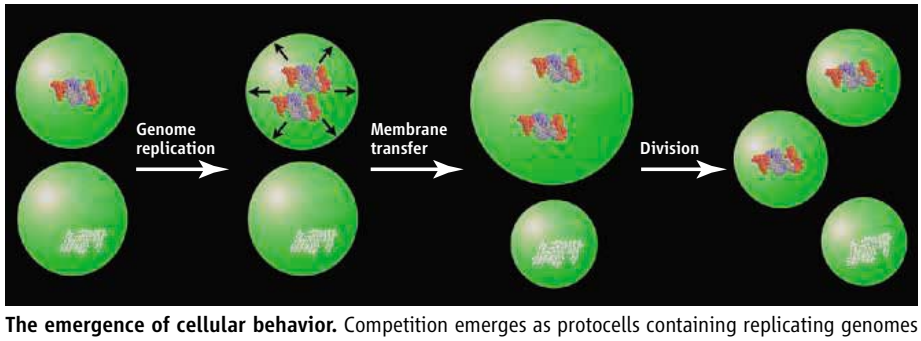
Modern living organisms are organized into cells. Fundamentally, a cell consists of a genome, which carries information, and a membrane, which separates the genome from the external environment. By segregating individual genomes from one another, cellular organization is thought to be critical to the evolution of replicating systems (*1*, *2*). Some of the oldest known rocks on Earth (~3.5 billion years old) contain biochemical signatures of life and also contain tantalizing suggestions of cellular fossils (*3*). But how did early self-replicating chemicals give rise to the "cell" as a unified entity? The combination of a genome and membrane does not constitute a unified cell unless interactions between the components result in mutual benefit. Was it a lucky accident that genomes and membranes began to cooperate with each other (e.g., evolution of an enzyme to synthesize membrane lipids)? Or are there simple physicochemical mechanisms that promote interactions between any genome and membrane, leading to the emergence of cellular behaviors? We explored such mechanisms experimentally, using model protocells.

A protocell could be constructed by encapsulating a self-replicating genome inside a chemically simple, self-replicating membrane (*1*). This minimalist, forward-engineering approach is akin to early evolution, which must have also used a minimal set of components. RNA is a particularly elegant genomic material, because it can act as both information carrier and enzyme [e.g., as an RNA polymerase (*4*)]. The discovery that the ribosome contains a catalytic ribozyme core lends considerable weight to the theory that an RNA world preceded the modern DNA-RNA-protein world (*5*–*7*). For the membrane, fatty acids are simple amphiphilic molecules that self-assemble into bilayer vesicles. These vesicles have interesting self-reproducing properties, including the ability to undergo multiple cycles of growth and division (*8*). Fatty acids have been synthesized under a variety of prebiotic conditions and have been found on meteorites (*9*–*11*). To validate this experimental model, we showed that the hammerhead ribozyme, which catalyzes a self-cleavage (or ligation) reaction, is active when encapsulated in vesicles composed of fatty acid (myristoleic acid) and its cognate glycerol monoester (*12*).

During the origin of life, what behavior would demonstrate the emergence of the cell as a new level of biological organization? A defining behavior of living systems is Darwinian evolution, which may act at any level, including that of the gene and the cell. Using model protocells, we observed a competition between vesicles encapsulating RNA and empty vesicles (*13*). Vesicles encapsulating high concentrations of RNA experienced substantial osmotic stress, driving the uptake of fatty acid from unstressed membranes. This resulted in the transfer of ~25% of the membrane from empty vesicles to vesicles containing RNA, relieving the membrane tension caused by the osmotic gradient. The growth of the osmotically stressed vesicles and the reduction of the unstressed vesicles were measured by the fluorescence resonance energy transfer (FRET) between fluorescent dyes incorporated into the membrane.

We suggest that a similar process took place during early evolution—vesicles encapsulating highly active genomic replicators would generate osmotic pressure, causing them to "steal" membrane from other vesicles containing less active sequences. Genomic fitness (i.e., replicative ability) would be translated into cellular fitness as the genome and membrane increased together, moving the evolutionary unit from the replicating molecule to the whole cell. As soon as replicators became encapsulated, a primitive form of competition could emerge between cells (see the figure). Remarkably, this process does not require a chance increase in complexity (e.g., addition of a new enzyme), but instead relies only on the physical properties of a semipermeable membrane encapsulating solute.

In a complementary experiment, we also demonstrated how membrane fitness (i.e., growth) might contribute to cellular fitness. Fatty acid vesicles can grow spontaneously by incorporation of a feedstock, such as fatty acid micelles (*14*). We found that membrane growth generated a transmembrane pH gradient, due to the faster flip-flop of protonated fatty acid molecules incorporated into the outer leaflet of the membrane (*15*). Acidification of the vesicle interior was measured by an encapsulated pH-sensitive fluorescent dye (pyranine). Thus, a protocell might capture a substantial fraction (~12%) of the energy released during membrane growth and store it in the form of a pH gradient. In modern biological systems, pH gradients are widely used for energy storage and transduction. For a protocell, this energy might even be directly useful for driving cellular processes, such as the



The emergence of cellular behavior. Competition emerges as protocells containing replicating genomes steal membrane from protocells containing inactive molecules.

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uptake of amines to aid RNA folding. Again, no additional enzymes need to be evolved for this basic form of energy capture and storage, which is only a consequence of the physical properties of the vesicles.

These results demonstrate that simple physicochemical properties of elementary protocells can give rise to essential cellular behaviors, including primitive forms of Darwinian competition and energy storage. Such preexisting, cooperative interactions between the membrane and encapsulated contents could greatly simplify the transition from replicating molecules to true cells. They also suggest intriguing possibilities for further investigation. For example, a corollary of vesicle competition is that a charged genetic polymer, such as nucleic acid, would be much more effective at driving membrane uptake than an electrically neutral polymer, because most of the osmotic pressure is due to counterions associated with the charged polymer. Could this influence the natural selection of the genetic material itself? Furthermore, competition for membrane molecules would favor stabilized membranes, suggesting a selective advantage for the evolution of cross-linked fatty acids (e.g., di- and triglycerides) and even the phospholipids of today. Greater membrane stability leads to decreased dynamics, however, and the evolutionary solutions to this problem (e.g., permeases, synthetic enzymes) could cause a "snowball" effect on the complexity of early life (*16*). Exploration of these minimal systems promises to lead to more exciting insights into the origins of biological complexity.

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10.1126/science.1137541

2006 Grand Prize Winner

Irene A. Chen, the author of the prize-winning essay and a North American regional winner, was born in San Diego, California, to Taiwanese-American parents. She has had a fascination with science from a young age. As a high school senior, she won the Westinghouse Science Talent Search for research done under the direction of Carol MacLeod of the University of California, San Diego. She majored in chemistry at Harvard University, and as an undergraduate studied molecular recognition in the laboratory of Gregory Verdine. Dr. Chen stayed at Harvard to enter the M.D.-Ph.D. program. Under the mentorship of Jack Szostak, she investigated the biophysics of the origin of life—work that was recognized with a 2005 Harold M. Weintraub Graduate Student Award. She is currently finishing medical school at Harvard and plans to continue to study molecules and evolution.

Regional Winners

North America: Dianne Schwarz for her essay "Unraveling the Mysteries of Small RNAs." Dr. Schwarz received a B.S. degree from the State University of New York at Albany. She did undergraduate research in the laboratory of Caro-Beth Stewart, where she studied the function of short interspersed repeats in primate DNA. As a graduate student in Phillip D. Zamore's lab at the University of Massachusetts Medical School in Worcester, she characterized the RNA interference (RNAi) pathway in *Drosophila* and humans and investigated possible therapeutic applications of RNAi to diseases such as amyotrophic lateral sclerosis. Dr. Schwarz's thesis work was recognized with a 2005 Harold M. Weintraub Graduate Student Award. She is currently a Jane Coffin Childs postdoctoral fellow in the lab of Erin K. O'Shea at Harvard University, where she studies stress response in yeast.

Europe: Bernhard Loll for his essay "Photosystem II, a Bioenergetic Nanomachine." Dr. Loll was born in Ravensburg, Germany. He studied chemistry at Albert-Ludwigs-Universität in Freiburg, Germany, and received his diploma in 2000. During this time he worked in the group of Georg E. Schulz, and this stimulated his interest in biochemistry and protein crystallography. He continued to follow these interests by pursuing Ph.D. work in the group of Wolfram Saenger at Freie Universität Berlin. There, Dr. Loll elucidated the three-dimensional structure of photosystem II, in work done in cooperation with the group of Athina Zouni at Technische Universität Berlin. Dr. Loll defended his Ph.D. in February 2005 and is currently a postdoctoral scientist in the group of Anton Meinhart at the Max-Planck-Institut für Medizinische Forschung in Heidelberg.

All Other Countries: Ron Milo for his essay "Simple Building Blocks for Complex Networks." Dr. Milo grew up in Kfar Saba, Israel. As an undergraduate he studied physics and mathematics at the Hebrew University in Jerusalem. His Ph.D. research, conducted under the guidance of Uri Alon at the Weizmann Institute of Science in Rehovot, centered on analyzing complex biological networks with the use of network motifs. Dr. Milo continued as a postdoctoral fellow in the Alon group, where he measured the variability and memory of protein levels in human cells. His doctoral research was recognized with a Dimitris N. Chorafas Foundation Award in 2004 and the institute's John F. Kennedy Award in 2006. Dr. Milo is currently a fellow in the Department of Systems Biology at Harvard Medical School. In his spare time he enjoys investigating the beauty of nature in New England together with his wife and daughter.

For the full text of essays by the regional winners and for information about applying for next year's awards, see *Science* Online at www.sciencemag.org/feature/data/prizes/ge/index.dtl.

Five Rules for the Evolution of Cooperation

Martin A. Nowak

Cooperation is needed for evolution to construct new levels of organization. Genomes, cells, multicellular organisms, social insects, and human society are all based on cooperation. Cooperation means that selfish replicators forgo some of their reproductive potential to help one another. But natural selection implies competition and therefore opposes cooperation unless a specific mechanism is at work. Here I discuss five mechanisms for the evolution of cooperation: kin selection, direct reciprocity, indirect reciprocity, network reciprocity, and group selection. For each mechanism, a simple rule is derived that specifies whether natural selection can lead to cooperation.

Evolution is based on a fierce competition between individuals and should therefore reward only selfish behavior. Every gene, every cell, and every organism should be designed to promote its own evolutionary success at the expense of its competitors. Yet we observe cooperation on many levels of biological organization. Genes cooperate in genomes. Chromosomes cooperate in eukaryotic cells. Cells cooperate in multicellular organisms. There are many examples of cooperation among animals. Humans are the champions of cooperation: From hunter-gatherer societies to nation-states, cooperation is the decisive organizing principle of human society. No other life form on Earth is engaged in the same complex games of cooperation and defection. The question of how natural selection can lead to cooperative behavior has fascinated evolutionary biologists for several decades.

A cooperator is someone who pays a cost, c, for another individual to receive a benefit, b. A defector has no cost and does not deal out benefits. Cost and benefit are measured in terms of fitness. Reproduction can be genetic or cultural. In any mixed population, defectors have a higher average fitness than cooperators (Fig. 1). Therefore, selection acts to increase the relative abundance of defectors. After some time, cooperators vanish from the population. Remarkably, however, a population of only cooperators has the highest average fitness, whereas a population of only defectors has the lowest. Thus, natural selection constantly reduces the average fitness of the population. Fisher's fundamental theorem, which states that average fitness increases under constant selection, does not apply here because selection is frequency-dependent: The fitness of individuals depends on the frequency (= relative abundance) of cooperators in the population. We see that natural selection in well-mixed populations needs help for establishing cooperation.

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Kin Selection

When J. B. S. Haldane remarked, "I will jump into the river to save two brothers or eight cousins," he anticipated what became later known as Hamilton's rule (*1*). This ingenious idea is that natural selection can favor cooperation if the donor and the recipient of an altruistic act are genetic relatives. More precisely, Hamilton's rule states that the coefficient of relatedness, r, must exceed the cost-to-benefit ratio of the altruistic act:

$$r > c/b \qquad (1)$$

Relatedness is defined as the probability of sharing a gene. The probability that two brothers share the same gene by descent is 1/2; the same probability for cousins is 1/8. Hamilton's theory became widely known as "kin selection" or "inclusive fitness" (*2*–*7*). When evaluating the fitness of the behavior induced by a certain gene, it is important to include the behavior's effect on kin who might carry the same gene. Therefore, the "extended phenotype" of cooperative behavior is the consequence of "selfish genes" (*8*, *9*).

Direct Reciprocity

It is unsatisfactory to have a theory that can explain cooperation only among relatives. We also observe cooperation between unrelated individuals or even between members of different species. Such considerations led Trivers (*10*) to propose another mechanism for the evolution of cooperation, direct reciprocity. Assume that there are repeated encounters between the same two individuals. In every round, each player has a choice between cooperation and defection. If I cooperate now, you may cooperate later. Hence, it might pay off to cooperate. This game theoretic framework is known as the repeated Prisoner's Dilemma.

But what is a good strategy for playing this game? In two computer tournaments, Axelrod (*11*) discovered that the "winning strategy" was the simplest of all, tit-for-tat. This strategy always starts with a cooperation, then it does whatever the other player has done in the previous round: a cooperation for a cooperation, a defection for a defection. This simple concept captured the fascination of all enthusiasts of the repeated Prisoner's Dilemma. Many empirical and theoretical studies were inspired by Axelrod's groundbreaking work (*12*–*14*).

But soon an Achilles heel of the world champion was revealed: If there are erroneous moves caused by "trembling hands" or "fuzzy minds," then the performance of tit-for-tat declines (*15*, *16*). Tit-for-tat cannot correct mistakes, because an accidental defection leads to a long sequence of retaliation. At first, tit-for-tat was replaced by generous-tit-for-tat (*17*), a strategy that cooperates whenever you cooperate, but sometimes cooperates although you have defected [with probability $1 - (c/b)$]. Natural selection can promote forgiveness.

Subsequently, tit-for-tat was replaced by win-stay, lose-shift, which is the even simpler idea of repeating your previous move whenever you are doing well, but changing otherwise (*18*). By various measures of success, win-stay, lose-shift is more robust than either tit-for-tat or generous-tit-for-tat (*15*, *18*). Tit-for-tat is an efficient catalyst of cooperation in a society where nearly everybody is a defector, but once cooperation is established, win-stay, lose-shift is better able to maintain it.

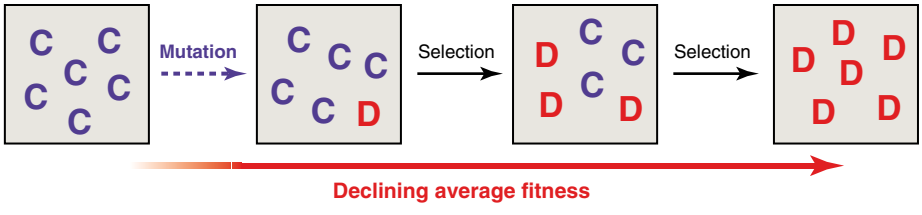

Fig. 1. Without any mechanism for the evolution of cooperation, natural selection favors defectors. In a mixed population, defectors, D, have a higher payoff (= fitness) than cooperators, C. Therefore, natural selection continuously reduces the abundance, i, of cooperators until they are extinct. The average fitness of the population also declines under natural selection. The total population size is given by N. If there are i cooperators and $N - i$ defectors, then the fitness of cooperators and defectors, respectively, is given by $f_C = [b(i - 1)/(N - 1)] - c$ and $f_D = bi/(N - 1)$. The average fitness of the population is given by $\bar{f} = (b - c)i/N$.

The number of possible strategies for the repeated Prisoner's Dilemma is unlimited, but a simple general rule can be shown without any difficulty. Direct reciprocity can lead to the evolution of cooperation only if the probability, w, of another encounter between the same two individuals exceeds the cost-to-benefit ratio of the altruistic act:

$$w > c/b \quad (2)$$

Indirect Reciprocity

Direct reciprocity is a powerful mechanism for the evolution of cooperation, but it leaves out certain aspects that are particularly important for humans. Direct reciprocity relies on repeated encounters between the same two individuals, and both individuals must be able to provide help, which is less costly for the donor than it is beneficial for the recipient. But often the interactions among humans are asymmetric and fleeting. One person is in a position to help another, but there is no possibility for a direct reciprocation. We help strangers who are in need. We donate to charities that do not donate to us. Direct reciprocity is like a barter economy based on the immediate exchange of goods, whereas indirect reciprocity resembles the invention of money. The money that fuels the engines of indirect reciprocity is reputation.

Helping someone establishes a good reputation, which will be rewarded by others. When deciding how to act, we take into account the possible consequences for our reputation. We feel strongly about events that affect us directly, but we also take a keen interest in the affairs of others, as demonstrated by the contents of gossip.

In the standard framework of indirect reciprocity, there are randomly chosen pairwise encounters where the same two individuals need not meet again. One individual acts as donor, the other as recipient. The donor can decide whether or not to cooperate. The interaction is observed by a subset of the population who might inform others. Reputation allows evolution of cooperation by indirect reciprocity (*19*). Natural selection favors strategies that base the decision to help on the reputation of the recipient. Theoretical and empirical studies of indirect reciprocity show that people who are more helpful are more likely to receive help (*20*–*28*).

Although simple forms of indirect reciprocity can be found in animals (*29*), only humans seem to engage in the full complexity of the game. Indirect reciprocity has substantial cognitive demands. Not only must we remember our own interactions, we must also monitor the ever-changing social network of the group. Language is needed to gain the information and spread the gossip associated with indirect reciprocity. Presumably, selection for indirect reciprocity and human language has played a decisive role in the evolution of human intelligence (*28*). Indirect reciprocity also leads to the evolution of morality (*30*) and social norms (*21*, *22*).

The calculations of indirect reciprocity are complicated and only a tiny fraction of this universe has been uncovered, but again a simple rule has emerged (*19*). Indirect reciprocity can only promote cooperation if the probability, q, of knowing someone's reputation exceeds the cost-to-benefit ratio of the altruistic act:

$$q > c/b \quad (3)$$

Network Reciprocity

The argument for natural selection of defection (Fig. 1) is based on a well-mixed population, where everybody interacts equally likely with everybody else. This approximation is used by all standard approaches to evolutionary game dynamics (*31*–*34*). But real populations are not well mixed. Spatial structures or social networks imply that some individuals interact more often than others. One approach of capturing this effect is evolutionary graph theory (*35*), which allows us to study how spatial structure affects evolutionary and ecological dynamics (*36*–*39*).

The individuals of a population occupy the vertices of a graph. The edges determine who interacts with whom. Let us consider plain cooperators and defectors without any strategic complexity. A cooperator pays a cost, c, for each neighbor to receive a benefit, b. Defectors have no costs, and their neighbors receive no benefits. In this setting, cooperators can prevail by forming network clusters, where they help each other. The resulting "network reciprocity" is a generalization of "spatial reciprocity" (*40*).

Games on graphs are easy to study by computer simulation, but they are difficult to analyze mathematically because of the enormous number of possible configurations that can arise. Nonetheless, a surprisingly simple rule determines whether network reciprocity can favor cooperation (*41*). The benefit-to-cost ratio must exceed the average number of neighbors, k, per individual:

$$b/c > k \quad (4)$$

Group Selection

Selection acts not only on individuals but also on groups. A group of cooperators might be more successful than a group of defectors. There have been many theoretical and empirical studies of group selection, with some controversy, and recently there has been a renaissance of such ideas under the heading of "multilevel selection" (*42*–*50*).

A simple model of group selection works as follows (*51*). A population is subdivided into groups. Cooperators help others in their own group. Defectors do not help. Individuals reproduce proportional to their payoff. Offspring are added to the same group. If a group reaches a certain size, it can split into two. In this case, another group becomes extinct in order to constrain the total population size. Note that only individuals reproduce, but selection emerges on two levels. There is competition between groups because some groups grow faster and split more often. In particular, pure cooperator groups grow faster than pure defector groups, whereas in any mixed group, defectors reproduce faster than cooperators. Therefore, selection on the lower level (within groups) favors defectors, whereas selection on the higher level (between groups) favors cooperators. This model is based on "group fecundity selection," which means that groups of cooperators have a higher rate of splitting in two. We can also imagine a model based on "group viability selection,"

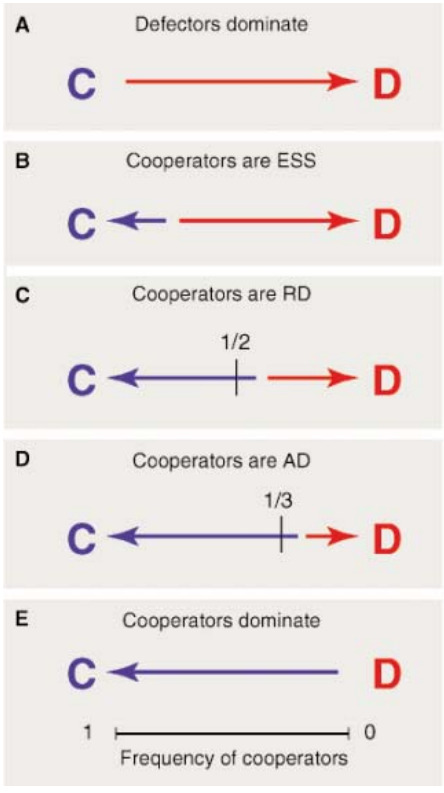

Fig. 2. Evolutionary dynamics of cooperators and defectors. The red and blue arrows indicate selection favoring defectors and cooperators, respectively. (**A**) Without any mechanism for the evolution of cooperation, defectors dominate. A mechanism for the evolution of cooperation can allow cooperators to be the evolutionarily stable strategy (ESS), risk-dominant (RD), or advantageous (AD) in comparison with defectors. (**B**) Cooperators are ESS if they can resist invasion by defectors. (**C**) Cooperators are RD if the basin of attraction of defectors is less than 1/2. (**D**) Cooperators are AD if the basin of attraction of defectors is less than 1/3. In this case, the fixation probability of a single cooperator in a finite population of defectors is greater than the inverse of the population size (for weak selection). (**E**) Some mechanisms allow cooperators to dominate defectors.

where groups of cooperators are less likely to go extinct.

In the mathematically convenient limit of weak selection and rare group splitting, we obtain a simple result (*51*): If n is the maximum group size and m is the number of groups, then group selection allows evolution of cooperation, provided that

$$b/c > 1 + (n/m) \quad (5)$$

Evolutionary Success

Before proceeding to a comparative analysis of the five mechanisms, let me introduce some measures of evolutionary success. Suppose a game between two strategies, cooperators C and defectors D, is given by the payoff matrix

	C	D
C	α	β
D	γ	δ

The entries denote the payoff for the row player. Without any mechanism for the evolution of cooperation, defectors dominate cooperators, which means $\alpha < \gamma$ and $\beta < \delta$. A mechanism for the evolution of cooperation can change these inequalities.

1) If $\alpha > \gamma$, then cooperation is an evolutionarily stable strategy (ESS). An infinitely large population of cooperators cannot be invaded by defectors under deterministic selection dynamics (*32*).

2) If $\alpha + \beta > \gamma + \delta$, then cooperators are risk-dominant (RD). If both strategies are ESS, then the risk-dominant strategy has the bigger basin of attraction.

3) If $\alpha + 2\beta > \gamma + 2\delta$, then cooperators are advantageous (AD). This concept is important for stochastic game dynamics in finite populations. Here, the crucial quantity is the fixation probability of a strategy, defined as the probability that the lineage arising from a single mutant of that strategy will take over the entire population consisting of the other strategy. An AD strategy has a fixation probability greater than the inverse of the population size, $1/N$. The condition can also be expressed as a 1/3 rule: If the fitness of the invading strategy at a frequency of 1/3 is greater than the fitness of the resident, then the fixation probability of the invader is greater than $1/N$. This condition holds in the limit of weak selection (*52*).

A mechanism for the evolution of cooperation can ensure that cooperators become ESS, RD, or AD (Fig. 2). Some mechanisms even allow cooperators to dominate defectors, which means $\alpha > \gamma$ and $\beta > \delta$.

Comparative Analysis

We have encountered five mechanisms for the evolution of cooperation (Fig. 3). Although the mathematical formalisms underlying the five mechanisms are very different, at the center of each theory is a simple rule. I now present a coherent mathematical framework that allows the derivation of all five rules. The crucial idea is that each mechanism can be presented as a game between two strategies given by a 2 × 2 payoff matrix (Table 1). From this matrix, we can derive the relevant condition for evolution of cooperation.

For kin selection, I use the approach of inclusive fitness proposed by Maynard Smith (*31*). The relatedness between two players is r. Therefore, your payoff multiplied by r is added to mine. A second method, shown in (*53*), leads to a different matrix but the same result. For direct reciprocity, the cooperators use tit-for-tat while the defectors use "always-defect." The expected number of rounds is $1/(1 - w)$. Two tit-for-tat players cooperate all the time. Tit-for-tat versus always-defect cooperates only in the first move and then defects. For indirect reciprocity, the probability of knowing someone's reputation is given by q. A cooperator helps unless the reputation of the other person indicates a defector. A defector never helps. For network reciprocity, it can be shown that the expected frequency of cooperators is described by a standard replicator equation with a transformed payoff matrix (*54*). For group selection, the payoff matrices of the two games—within

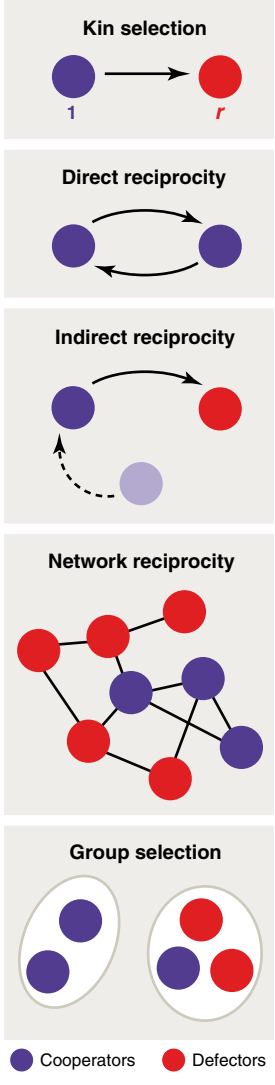

Fig. 3. Five mechanisms for the evolution of cooperation. Kin selection operates when the donor and the recipient of an altruistic act are genetic relatives. Direct reciprocity requires repeated encounters between the same two individuals. Indirect reciprocity is based on reputation; a helpful individual is more likely to receive help. Network reciprocity means that clusters of cooperators outcompete defectors. Group selection is the idea that competition is not only between individuals but also between groups.

Table 1. Each mechanism can be described by a simple 2 × 2 payoff matrix, which specifies the interaction between cooperators and defectors. From these matrices we can directly derive the necessary conditions for evolution of cooperation. The parameters c and b denote, respectively, the cost for the donor and the benefit for the recipient. For network reciprocity, we use the parameter $H = [(b - c)k - 2c]/[(k + 1)(k - 2)]$. All conditions can be expressed as the benefit-to-cost ratio exceeding a critical value. See (*53*) for further explanations of the underlying calculations.

		Payoff matrix		Cooperation is...			
		C	D	ESS	RD	AD	
Kin selection	C	$(b-c)(1+r)$	$br-c$	$\frac{b}{c} > \frac{1}{r}$	$\frac{b}{c} > \frac{1}{r}$	$\frac{b}{c} > \frac{1}{r}$	r...genetic relatedness
	D	$b-rc$	0				
Direct reciprocity	C	$(b-c)/(1-w)$	$-c$	$\frac{b}{c} > \frac{1}{w}$	$\frac{b}{c} > \frac{2-w}{w}$	$\frac{b}{c} > \frac{3-2w}{w}$	w...probability of next round
	D	b	0				
Indirect reciprocity	C	$b-c$	$-c(1-q)$	$\frac{b}{c} > \frac{1}{q}$	$\frac{b}{c} > \frac{2-q}{q}$	$\frac{b}{c} > \frac{3-2q}{q}$	q...social acquaintanceship
	D	$b(1-q)$	0				
Network reciprocity	C	$b-c$	$H-c$	$\frac{b}{c} > k$	$\frac{b}{c} > k$	$\frac{b}{c} > k$	k...number of neighbors
	D	$b-H$	0				
Group selection	C	$(b-c)(m+n)$	$(b-c)m-cn$	$\frac{b}{c} > 1+\frac{n}{m}$	$\frac{b}{c} > 1+\frac{n}{m}$	$\frac{b}{c} > 1+\frac{n}{m}$	n...group size m...number of groups
	D	bn	0				

and between groups—can be added up. The details of all these arguments and their limitations are given in (*53*).

For kin selection, the calculation shows that Hamilton's rule, $r > c/b$, is the decisive criterion for all three measures of evolutionary success: ESS, RD, and AD. Similarly, for network reciprocity and group selection, we obtain the same condition for all three evaluations, namely $b/c > k$ and $b/c > 1 + (n/m)$, respectively. The reason is the following: If these conditions hold, then cooperators dominate defectors. For direct and indirect reciprocity, we find that the ESS conditions lead to $w > c/b$ and $q > c/b$, respectively. Slightly more stringent conditions must hold for cooperation to be RD or AD.

Conclusion

Each of the five possible mechanisms for the evolution of cooperation—kin selection, direct reciprocity, indirect reciprocity, network reciprocity and group selection—can be described by a characteristic 2×2 payoff matrix, from which we can directly derive the fundamental rules that specify whether cooperation can evolve (Table 1). Each rule can be expressed as the benefit-to-cost ratio of the altruistic act being greater than some critical value. The payoff matrices can be imported into standard frameworks of evolutionary game dynamics. For example, we can study replicator equations for games on graphs (*54*), for group selection, and for kin selection. This creates interesting new possibilities for the theory of evolutionary dynamics (*55*).

I have not discussed all potential mechanisms for the evolution of cooperation. An interesting possibility is offered by "green beard" models where cooperators recognize each other via arbitrary labels (*56*–*58*). Another way to obtain cooperation is making the game voluntary rather than obligatory: If players can choose to cooperate, defect, or not play at all, then some level of cooperation usually prevails in dynamic oscillations (*59*). Punishment is an important factor that can promote cooperative behavior in some situations (*60*–*64*), but it is not a mechanism for the evolution of cooperation. All evolutionary models of punishment so far are based on underlying mechanisms such as indirect reciprocity (*65*), group selection (*66*, *67*), or network reciprocity (*68*). Punishment can enhance the level of cooperation that is achieved in such models.

Kin selection has led to mathematical theories (based on the Price equation) that are more general than just analyzing interactions between genetic relatives (*4*, *5*). The interacting individuals can have any form of phenotypic correlation. Therefore, kin selection theory also provides an approach to compare different mechanisms for the evolution of cooperation (*69*, *70*).

The two fundamental principles of evolution are mutation and natural selection. But evolution is constructive because of cooperation. New levels of organization evolve when the competing units on the lower level begin to cooperate. Cooperation allows specialization and thereby promotes biological diversity. Cooperation is the secret behind the open-endedness of the evolutionary process. Perhaps the most remarkable aspect of evolution is its ability to generate cooperation in a competitive world. Thus, we might add "natural cooperation" as a third fundamental principle of evolution beside mutation and natural selection.

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Supporting Online Material

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Ebola Outbreak Killed 5000 Gorillas

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Over the past decade, the Zaire strain of Ebola virus (ZEBOV) has emerged repeatedly in Gabon and Congo. During each human outbreak, carcasses of western gorillas (*Gorilla gorilla*) and chimpanzees (*Pan troglodytes*) have been found in neighboring forests (*1*). Opinions have differed as to the conservation implications. Were these isolated mortality events of limited impact (*2*)? Was ZEBOV even the cause (*3*)? Or, were they part of a massive die-off that threatens the very survival of these species (*4*)? Here, we report observations made at the Lossi Sanctuary in northwest Republic of Congo, where ZEBOV was the confirmed cause of ape die-offs in 2002 and 2003 (*5*). Our results strongly support the massive die-off scenario, with gorilla mortality rates of 90 to 95% indicated both by observations on 238 gorillas in known social groups and by nest surveys covering almost 5000 km^2. ZEBOV killed about 5000 gorillas in our study area alone.

Starting in 1995, we habituated gorillas to our presence, and by 2002 we had identified 10 social groups with 143 individuals (fig. S1). In late 2001 and early 2002, human outbreaks of ZEBOV had flared up along the Gabon-Congo border (*1*). In June 2002, a gorilla carcass was found 15 km west of the sanctuary. By October, gorilla and chimpanzee carcasses began appearing inside the sanctuary. In the next 4 months, we found 32 carcasses. Twelve of the carcasses were assayed for ZEBOV, and 9 tested positive (*5*). From October 2002 to January 2003, 91% (130/143) of the individually known gorillas in our study groups had disappeared.

In June 2003, one fresh carcass appeared south of the sanctuary. In September, we identified seven new social groups with home ranges straddling and to the east of the two rivers and monitored their sleeping nests on a biweekly basis. Then in October carcasses again appeared within the sanctuary. Ten carcasses were found in the following 3 months. From October 2003 to January 2004, Ebola spread sequentially from north to south, killing 91 of the 95 individuals (95.8%) in the newly monitored groups. One remarkable feature of this spread was that the onset of ZEBOV deaths in each group was predicted by the number of home ranges separating it from the first group to experience deaths (Fig. 1A). In particular, the estimated time lag between deaths in successive groups (11.2 days) was very similar to the typical length of the ZEBOV disease cycle of about 12 days (*6*). Assuming deaths were caused by spillover from a north-south reservoir epizootic did not fit the mortality pattern well (Fig. 1B). This implies that recent ape die-offs may not have been caused only by massive spillover from a reservoir host (*1*, *5*). Rather, group-to-group transmission may have also played a role in amplifying outbreaks, as transmission within gorilla groups apparently has (*7*).

The location of carcasses at the end of 2002 suggested a sharp mortality frontier running north to south at about longitude 14.55°E. The late-2003 outbreak reemerged along this frontier, but nest surveys conducted in 2004 and 2005 suggest that it affected only a limited enclave centered on our study site. High gorilla densities still persist in much of the region to the east of the 14.55°E frontier, but to the west a zone covering at least 2700 km^2 was largely emptied of gorillas, with nest encounter rates 96% lower than in the east (Fig. 1C). This encounter rate difference is not explained well by hunting, because the western zone experienced substantially lower hunting pressure than that in the eastern zone (table S1).

If we conservatively assume that the western zone held pre-Ebola ape densities only half as high as the 4.4 gorillas/km^2 typical of the sanctuary, then the east-west difference in nest encounter rate implies that ZEBOV killed about 5500 [minimum 3500 (Materials and Methods)]. We lack the density data necessary to make a similar estimate for chimpanzees, but east-west differences in nest encounter rate (Fig. 1D) imply a ZEBOV-induced decline of about 83% (table S1).

We hope this study dispels any lingering doubts that ZEBOV has caused massive gorilla die-offs. The Lossi outbreaks killed about as many gorillas as survive in the entire eastern gorilla species (*Gorilla beringei*). Yet Lossi represents only a small fraction of the western gorillas killed by ZEBOV in the past decade or indeed of the number at high risk in the next 5 years. Add commercial hunting to the mix, and we have a recipe for rapid ecological extinction. Ape species that were abundant and widely distributed a decade ago are rapidly being reduced to tiny remnant populations.

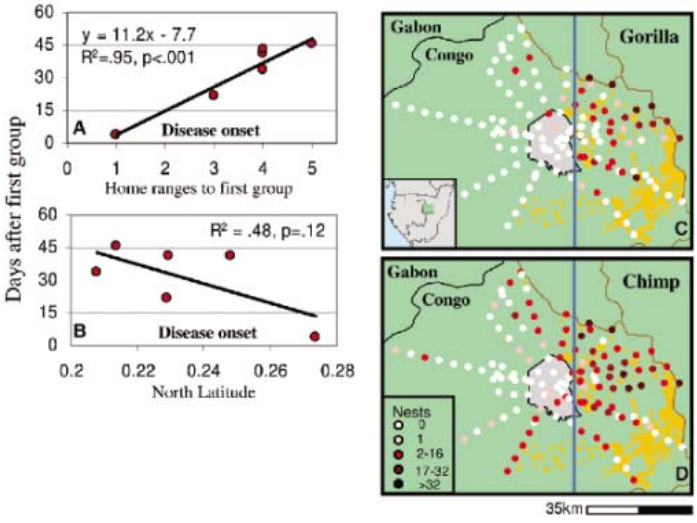

Fig. 1. (**A**) Last day at which each group was at full size plotted against number of home ranges separating that group from the first group to suffer deaths. (**B**) Day of last full group size was not well predicted by latitude, as might be expected with spillover from a north-to-south reservoir epizootic. Assuming other reservoir epizootic trajectories did not improve fit. (**C**) Gorilla nest distribution during 2004 to 2005 surveys (after ZEBOV die-offs). Shading of each dot proportional to number of gorilla nests found on a 5-km survey segment. Blue line at 14.55°E longitude separates eastern from western sampling zone. Lossi Sanctuary in gray, savannas in yellow, and roads in brown. (**D**) Chimpanzee nest distribution in 2004 to 2005 surveys.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5805/1564/DC1
Materials and Methods
Fig. S1
Table S1
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Movie S1

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Engineering Yeast Transcription Machinery for Improved Ethanol Tolerance and Production

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Global transcription machinery engineering (gTME) is an approach for reprogramming gene transcription to elicit cellular phenotypes important for technological applications. Here we show the application of gTME to *Saccharomyces cerevisiae* for improved glucose/ethanol tolerance, a key trait for many biofuels programs. Mutagenesis of the transcription factor Spt15p and selection led to dominant mutations that conferred increased tolerance and more efficient glucose conversion to ethanol. The desired phenotype results from the combined effect of three separate mutations in the *SPT15* gene [serine substituted for phenylalanine ($Phe^{177}Ser$) and, similarly, $Tyr^{195}His$, and $Lys^{218}Arg$]. Thus, gTME can provide a route to complex phenotypes that are not readily accessible by traditional methods.

The production of desirable compounds from microbes can often require a complete reprogramming of their innate metabolism. The evolution of such complex traits requires simultaneous modification in the expression levels of many genes, which may not be achievable by sequential multigene modifications. Furthermore, the identification of genes requiring perturbation may be largely unanticipated by conventional pathway analysis. The cellular engineering approach termed "global transcription machinery engineering" (gTME) alters [via error-prone polymerase chain reaction (PCR) mutations] key proteins regulating the global transcriptome and generates, through them, a new type of diversity at the transcriptional level.

This approach has already been demonstrated by engineering sigma factors in prokaryotic cells (*1*), but the increased complexity of eukaryotic transcription machinery raises the question of whether gTME can be used to improve traits in more complex organisms. For example, eukaryotic systems have more specialization—three RNA polymerase enzymes with separate functions, whereas only one exists in prokaryotes. Moreover, nearly 75 components have been classified as general transcription factors or coactivators of the RNA polymerase II (RNA Pol II) system (*2*), and loss of function for many of these components is lethal. Components of the general factor RNA Pol II transcription factor D (TFIID) include the TATA-binding protein (*SPT15*) and 14 other associated factors (TAFs) that are collectively thought to be the main DNA binding proteins regulating promoter specificity in yeast (*2*–*5*). Mutations in a TATA-binding protein have been shown to change the preference of the three polymerases and to play an important role in promoter specificity (*6*).

Successful fermentations to produce ethanol using yeast require tolerance to high concentrations of both glucose and ethanol. These cellular characteristics are important because very high gravity (VHG) fermentations, which are common in the ethanol industry, give rise to high sugar concentrations (and thus high osmotic pressure), at the beginning of the process, and high ethanol concentration at the end of a batch (*7*, *8*). As with ethanol tolerance in *Escherichia coli*, tolerance to ethanol and glucose mixtures does not seem to be a monogenic trait (*9*). Therefore, traditional methods of strain improvement have had limited success beyond the identification of medium supplementations and various chemical protectants (*10*–*14*).

To evaluate the approach of gTME in a eukaryotic system, two gTME mutant libraries were created from either *SPT15* (which encodes the TATA-binding protein) or one of the TATA-binding protein–associated factors, in this case, *TAF25* (*15*). The yeast screening and selection was performed in the background of the standard haploid *Saccharomyces cerevisiae* strain BY4741, which contains the endogenous, unmutated chromosomal copy of *SPT15* and *TAF25*. As such, this genetic screen uses a strain that expresses both the wild-type and mutated versions of the protein and, thus, permits the identification of dominant mutations that lead to novel functions in the presence of the unaltered chromosomal gene. These libraries were transformed into yeast and were selected in the presence of elevated levels of ethanol and glucose. The *spt15* mutant library showed modest growth in the presence of 5% ethanol and 100 g/liter of glucose, so the stress was increased in the subsequent serial subculturing to 6% ethanol and 120 g/liter of glucose. After the subculturing, strains were isolated from plates, and plasmids containing mutant genes were isolated and retransformed into a fresh background, then tested for their capacity to grow in the presence of elevated glucose and ethanol levels. The best mutant obtained from each of these two libraries was assayed in further detail and sequenced.

The sequence characteristics of these altered genes conferring the best properties (one Spt15p and one Taf25p) are shown in Fig. 1A. Each of these mutated genes contained three mutations, with those of *spt15* localized to the second repeat element, which consists of a set of β sheets (*5*, *16*). These specific triple mutations in the *taf25* and *spt15* mutant genes are thus referred to as the *taf25-300* and *spt15-300* mutations.

The *spt15-300* mutant outperformed the control at all concentrations tested, with the strain harboring the mutant protein providing up to 13-fold improvement in growth yield at some glucose concentrations (Fig. 1B and fig. S1). The *taf25-300* mutant was unable to grow in the presence of 6% ethanol, consistent with the observations seen during the enrichment and selection phase. Despite these increases in tolerance, the basal growth rate of these mutants in the absence of ethanol and glucose stress was similar to that of the control. Furthermore, the differences in behavior between the *spt15-300* mutant and *taf25-300* mutant suggest that mutations in genes encoding different members of the eukaryotic transcription machinery are likely to elicit different (and unanticipated) phenotypic responses.

The remainder of this study focuses on the *spt15-300* mutant, because this triple mutation set, in which serine is substituted for phenylalanine ($Phe^{177}Ser$), and similarly, $Tyr^{195}His$, and $Lys^{218}Arg$ (F177S, Y195H, and K218R, respectively), provided the most desirable phenotype with respect to elevated ethanol and glucose. At ethanol concentrations above 10%, the *spt15-300* mutant exhibited statistically significantly improved cellular viability (over the course of 30 hours of culturing) above that of the control, even at concentrations as high as 20% ethanol by volume (Fig. 2, A and B, and fig. S2).

Transcriptional profiling revealed that the mutant *spt15-300* exhibited differential expression of hundreds of genes [controlled for false discovery (*17*)] in the unstressed condition (0% ethanol and 20 g/liter glucose) relative to cells expressing the wild-type *SPT15* (*18*). This analysis mainly used the unstressed condition, rather than the stressed (5% ethanol and 60 g/liter

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glucose), because expression ratios were more reliable under this condition owing to the similarity of growth rates, which made gene expression profiles more comparable (SOM text, part c, and table S3). It is noted that the impact of the ethanol and glucose stress had a variable effect on many of the genes, and often, the stress did not further affect many of the genes selected using unstressed conditions (SOM text, part c). Although this widespread alteration in transcription is similar to that observed in *E. coli* with an altered sigma factor, the majority of the genes with altered expression are up-regulated, unlike the balanced distribution seen with *E. coli* (SOM text, part b, and fig. S3). The transcriptional reprogramming in the *spt15-300* mutant was quite broad, yet it exhibited some enrichment of certain functional groups such as oxidoreductase activity, cytoplasmic proteins, amino acid metabolism, and electron transport (SOM text, part b, and fig S4). Unclassified genes or genes with no known function were also found with higher levels of expression. An analysis of promoter-binding sites, as well as a search for active gene subnetworks using the Cytoscape (*19*) framework, failed to show that a particular pathway or genetic network was predominately responsible for the observed genetic reprogramming (*15*).

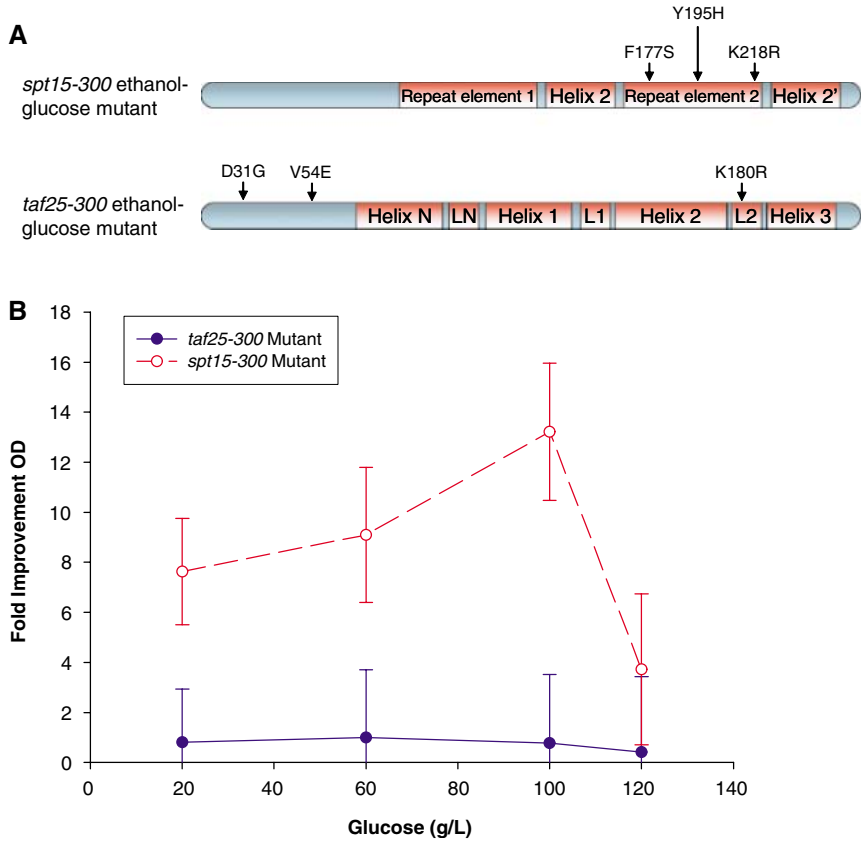

Fig. 1. Yeast gTME mutants with increased tolerance to elevated ethanol and glucose concentrations. (**A**) Mutations for the best clone isolated from either the *spt15* or *taf25* mutant library are shown mapped onto a schematic of critical functional components of the respective factor (SOM text, part a). (**B**) Growth yields of the clones from (A), were assayed in synthetic minimal medium containing elevated levels (6% by volume) of ethanol and glucose after 20 hours. Under these conditions, the *spt15-300* mutant far exceeded the performance of the *taf25-300* mutant. Fold improvements of growth yields are compared with an isogenic strain that harbors a plasmid-borne, wild-type version of either *SPT15* or *TAF25*.

To determine whether these up-regulated genes acted individually or as an ensemble to provide increased ethanol and glucose tolerance, we examined the effect of individual gene knockouts on the phenotype. Twelve of the most highly expressed genes in the mutant under the unstressed conditions of 0% ethanol and 20 g/liter of glucose were selected along with two additional genes (SOM text, part c, and tables S2 and S3). The results of the loss-of-phenotype assay are summarized in Fig. 3A. They show that deletion of the great majority of the overexpressed gene targets resulted in a loss of the capacity of the mutant *spt15-300* factor to impart an increased ethanol and glucose tolerance. All tested knockout strains not harboring the mutant *spt15-300* showed normal tolerance to ethanol and glucose stress, which indicated

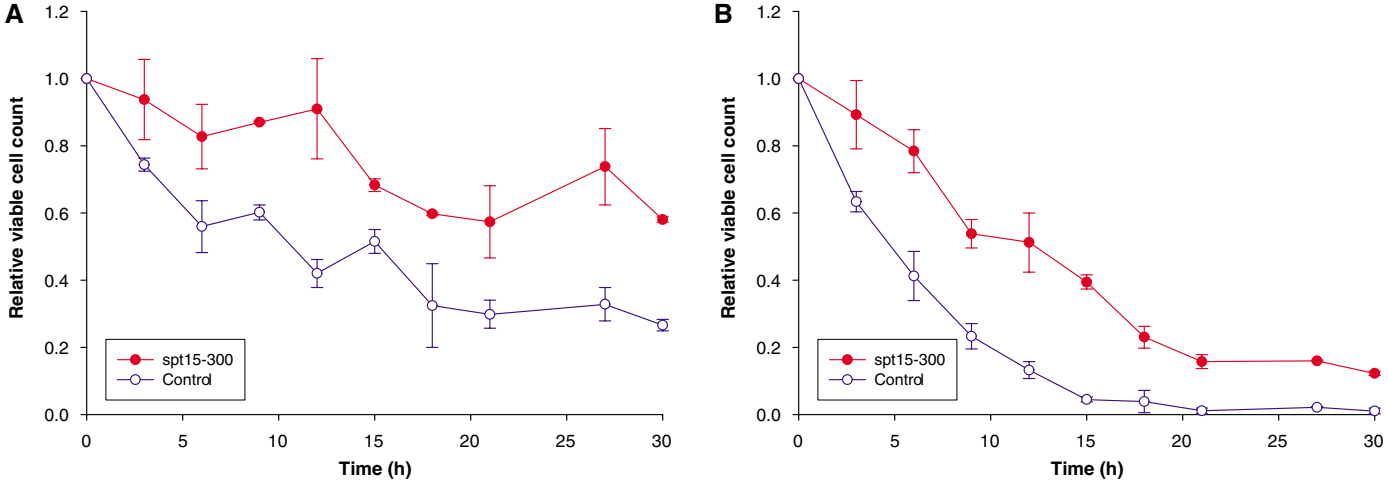

Fig. 2. Cellular viability curves to evaluate the tolerance of the mutant under ethanol stress. Viability of the *spt15-300* mutant strain compared with the control is measured as a function of time (hours) and expressed as the relative number of colony-forming units compared with colony count at 0 hours for stationary phase cells treated and incubated in standard medium in the presence of (**A**) 12.5% and (**B**) 15% ethanol by volume. The *spt15-300* mutation confers a significantly enhanced viability at all concentrations tested above 10% ethanol by volume (fig. S2). Error bars represent the standard deviation between biological replicate experiments. Initial cell counts were ~3.5 × 10^6 cells per ml.

that, individually, these genes are insufficient to constitute the normal tolerance to ethanol. Out of the 14 gene targets assayed, only loss of *PHM6* function did not reduce the novel phenotype. Thus, we hypothesize that each gene encodes a necessary component of an interconnected network, although there may be some redundancy of function (SOM text, part c).

Three genes that exhibited the greatest increase in expression level in the *spt15-300* mutant were investigated as overexpression targets in the control strain in a gain-of-function assay. *PHO5*, *PHM6*, and *FMP16* were independently and constitutively overexpressed under the control of the *TEF* promoter, and transformants were assayed for their capacity to impart an ethanol- and glucose-tolerance phenotype. Overexpression of no single gene among the consensus, top-candidate genes from the microarray analysis produced a gain of phenotype similar to that of the mutant *spt15-300* (Fig. 3B).

We next constructed all possible single- and double-mutant combinations with the sites identified in the triple mutant (*15*). None of the single or double mutants came even close to achieving a phenotype similar to that of the isolated *spt15-300* triple mutant (SOM text, part d, and figs. S6 to S8). One could not predict the effect of these three mutations by a "greedy algorithm" search approach or select these by traditional selection for mutations that cause incremental improvement, as many of these isolated mutations are independently relatively neutral in phenotype fitness. Consequently, such a multiple mutant is accessible only through a technique that specifically focuses on the in vitro mutagenesis of the *SPT15* gene followed by a demanding selection.

Genes previously documented as *SPT3*-dependent in expression (*20*, *21*) were preferentially altered by our *spt15* mutant, as exhibited in the microarray data, with a Bonferroni-corrected *P* value of 1×10^{-12}. Furthermore, 7 of the 10 most highly expressed genes in the *spt15-300* mutant are *SPT3*-dependent genes. Genes that are down-regulated in *spt3* mutants were rela-

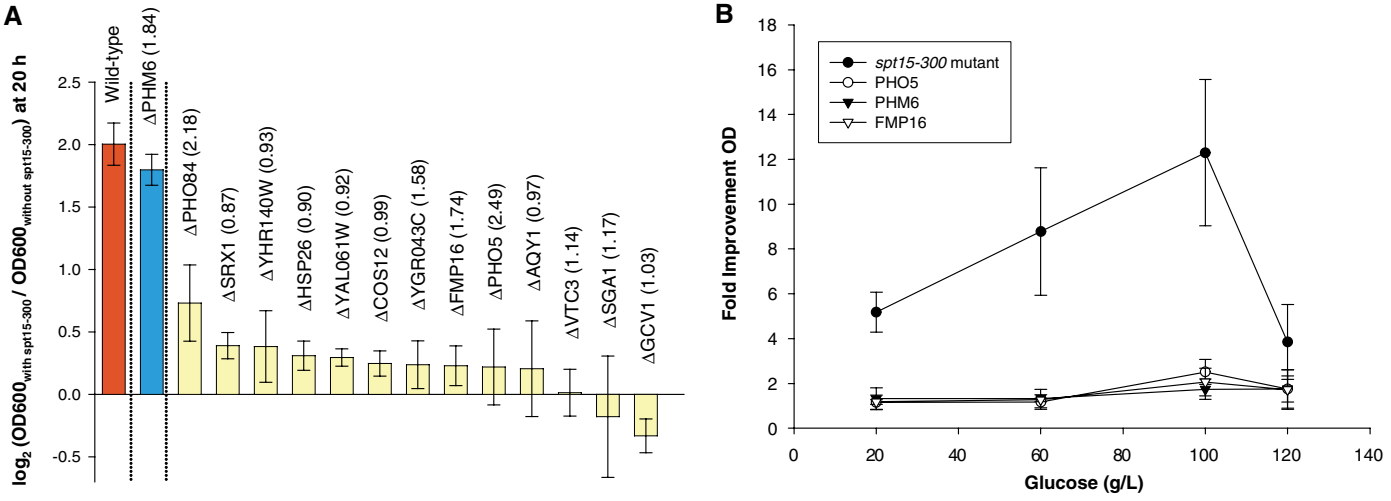

Fig. 3. Gene-knockout and overexpression analysis to probe the transcriptome-level response elicited by the mutant *spt15*. (**A**) Loss-of-phenotype analysis was performed using 12 of the most highly expressed genes in this mutant ($\log_2$ differential gene expression given in parentheses); two additional genes were chosen for further study (SOM text, part c). The tolerance (to 5% ethanol, 60 g/liter glucose) of 14 strains deleted in one of the 14 genes, respectively, was tested by comparing the knockout strain containing the *spt15-300* mutation on a plasmid to a strain containing the wild-type *SPT15*. All gene knockouts, except *PHM6,* resulted in slight to full loss of phenotype. Control mutants for all of the gene knockout targets exhibited similar growth yields. (**B**) Gene overexpression studies are provided for the top three candidate genes from the microarray (*PHO5*, *PHM6*, and *FMP*16) and assayed under 6% ethanol by volume as previously assayed (see also fig. S5). The overexpression of these genes failed to impart a tolerance phenotype.

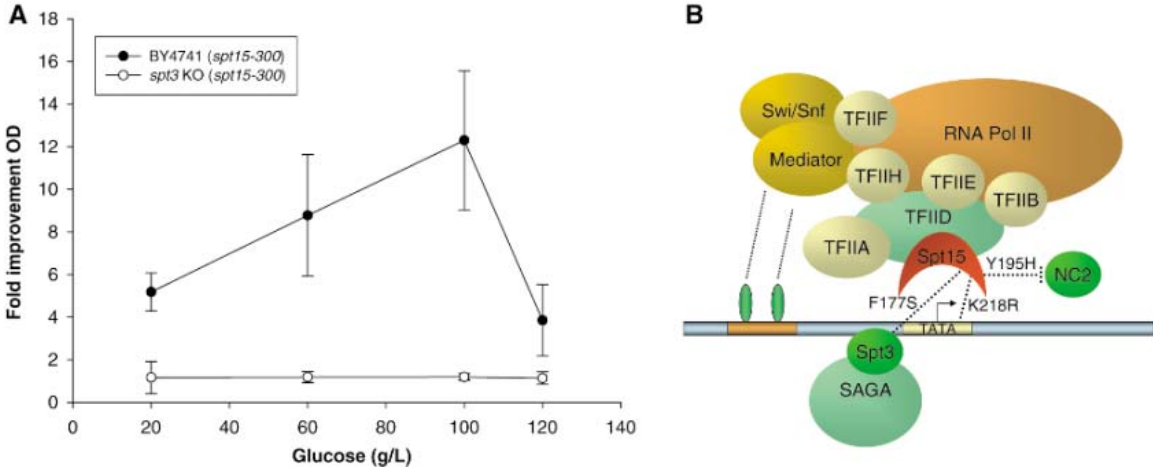

Fig. 4. Elucidation and validation of a mechanism partially mediated by the *SPT3*-SAGA complex. (**A**) The impact of an *spt3* knockout was evaluated through the introduction of the *spt15-300* mutant and assaying in the presence of 6% ethanol by volume. The incapacity of the mutant to impart the phenotype illustrates the essentiality of *SPT3* as a part of the mechanism provided. (**B**) The three mutations (F177S, Y195H, and K218R) are mapped on the global transcription machinery molecular mechanism proposed by prior studies, with each of these mutation sites (*22*–*24*, *27*, *28*). Collectively, these three mutations lead to a mechanism involving Spt3p.

tively up-regulated in the *spt15-300* mutant. The absence of negative cofactor 2 element (NC2) repression due to the Y195H mutation (*22*) may result in overrepresentation of up-regulated genes, because part of the negative regulation of the Spt15p can no longer take place. These data are consistent with previous work showing that the *spt15-21* mutation [a change from Ser to Leu or Arg at Phe^{177} (F177L and F177R)] suppresses an *spt3* mutation as the result of an altered interaction between the Spt15p and Spt3p [part of the Spt-Ada-Gcn5-acetyltransferase (SAGA) complex] (*21*, *23*, *24*). As a further test of the link between Spt15p and Spt3p, it was found that an *spt15-300* mutant gene was unable to impart its ethanol- and glucose-tolerance phenotype to an *spt3* knockout strain (Fig. 4A).

From the results of the site-directed mutagenesis and mechanism depicted in Fig. 4B, it is conceivable that perturbations to the NC2 complex would also impact the ability of the *spt15-300* mutant to function; however, a null mutation in one of the genes in this heterodimer is inviable, which prevents such a follow-up experiment. Nevertheless, these results further underscore the importance of all three mutations acting in concert in order to create the complex phenotype mediated through an Spt3p-SAGA complex interaction. As a result, we posit that the mode of action is primarily a unique protein–protein–DNA interaction (Spt15-300p mutant–Spt3p–DNA), which leads to this transcriptional reprogramming of a large number of genes.

The capacity of the *spt15-300* mutant to use and ferment glucose to ethanol under a variety of conditions was assayed in simple batch shake-flask experiments of low and high cell density under an initial concentration of 20 or 100 g/liter of glucose (SOM text, part e, and figs. S9 to S11). In each of these cases, the mutant has growth characteristics superior to those of the control with a prolonged exponential growth phase that allows for a higher, more robust biomass production and a higher ethanol yield. Specifically, in high–cell density fermentations, with an initial optical density at 600 nm (OD_{600}) of 15, the mutant's performance far exceeds that of the control, with more rapid utilization of glucose, improved biomass yield, and higher volumetric ethanol productivity (2 g/liter of ethanol per hour) relative to the control strain (Table 1). In addition, sugars were rapidly and fully used at a yield that exceeds that of the control and approaches the theoretical value when taking into account the amount of glucose consumed for cell growth.

These results demonstrate the applicability of gTME to alter cellular eukaryotic phenotypes. The isolation of dominant mutations permits the modification of vital functions for novel tasks, whereas the unmodified allele carries out the functions critical for viability. An examination of further modifications of other transcription factors through gTME could additionally have the potential for drastically improving ethanol fermentations and for improving the prospects of ethanol production. For the mutants analyzed, altered fermentation conditions and additional pathway engineering are likely to further increase ethanol production (*25*, *26*). Furthermore, the strain used in this study is a standard laboratory yeast strain, and this method could be explored in industrial or isolated yeast exhibiting naturally higher starting ethanol tolerances. Finally, we note that the transcription factors modified in this study have similarity to those in more complex eukaryotic systems including those of mammalian cells, which raises the possibility of using this tool to elicit complex phenotypes of both biotechnological and medical interest in these systems as well.

Table 1. Fermentation results to evaluate the ethanol production potential of the *spt15* mutant. Cells were cultured in biological replicate in 100 g/liter of glucose with a high inoculum of initial cell optical density of (OD_{600}) of 15 [~4 g DCW(dry cell weight)/liter]. Fermentation profiles for the high–cell density fermentation are provided and illustrate the capacity of this mutant to produce higher productivities of ethanol at the theoretical yield, surpassing the function of the control. Biomass yield from glucose is from reported values (*29*). Results represent the average between biological replicate experiments (SOM text, part e, and figs. S9 to S11). EtOH, ethanol.

Parameter	*spt15-300* mutant	Control	Percent improvement
Initial DCW (g/liter)	4.06	4.10	—
Final DCW(g/liter)	6.46	5.39	+20%
Volumetric productivity (g/liter h^{-1})	2.03	1.20	+69%
Specific productivity (g/DCW h^{-1})	0.31	0.22	+41%
Conversion yield calculated between 6 and 21 hours	0.36	0.32	+14%
True EtOH yield accounting for biomass production (Percentage of 0.41 g/g, which represents the theoretical maximum)	0.40 (98%)	0.35 (86%)	+15%

$$\frac{\text{EtOH produced (g/liter)}}{\text{glucose used (g/liter)} - \left(\frac{1\text{ g glucose}}{0.5\text{ g DCW}}\right)\text{DCW produced (g/liter)}}$$

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Supporting Online Material

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Group Competition, Reproductive Leveling, and the Evolution of Human Altruism

Samuel Bowles

Humans behave altruistically in natural settings and experiments. A possible explanation—that groups with more altruists survive when groups compete—has long been judged untenable on empirical grounds for most species. But there have been no empirical tests of this explanation for humans. My empirical estimates show that genetic differences between early human groups are likely to have been great enough so that lethal intergroup competition could account for the evolution of altruism. Crucial to this process were distinctive human practices such as sharing food beyond the immediate family, monogamy, and other forms of reproductive leveling. These culturally transmitted practices presuppose advanced cognitive and linguistic capacities, possibly accounting for the distinctive forms of altruism found in our species.

Darwin thought that the "moral faculties" had proliferated among early humans because a tribe of "courageous, sympathetic and faithful members who were always ready to…aid and defend each other… would spread and be victorious over other tribes" (*1*, p. 134). Recent experiments have extensively documented altruistic behaviors not only in laboratories but also among hunter-gatherer populations (*2*–*4*). But in order for the survival of more altruistic groups in competition with other groups to account for the evolution of a predisposition to act altruistically, the group extinction process would have to be strong enough to offset the lower fitness of altruists compared to other members of their group. For this to be the case, there would have to be substantial differences in the fraction of altruists in groups, which is thought to be unlikely because migration among groups tends to limit between-group differences in group composition. Thus, many have concluded that between-group genetic differences are too small for selective group extinction to offset the within-group selective pressures that oppose the evolution of a genetic predisposition to behave altruistically [(*5*), but see also (*6*)].

However, early humans lived under conditions such that selective group extinction might have been a powerful evolutionary force. Culturally transmitted norms supporting resource and information sharing, consensus decision-making, collective restraints on would-be aggrandizers, monogamy, and other reproductive leveling practices that reduced within-group differences in fitness may have attenuated the selective pressures to which altruists are subject (*7*–*11*). The impact of intergroup competition is heightened by the fact that although group aggression is not uniquely human (*12*), among humans it is extraordinarily lethal (*13*).

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Models (*14*), computer simulations (*15*), and empirical studies (*16*) have confirmed that intergroup competition could influence the evolution of culturally transmitted behavior. This study investigates whether, as an empirical matter, intergroup competition and reproductive leveling might have allowed the proliferation of a genetically transmitted predisposition to behave altruistically. To determine the facts necessary for this inquiry, a model was developed that captures the main aspects of ancestral human genetic differentiation, between-group competition, and group social structure.

Framework for the empirical analysis. Consider a large metapopulation of individuals living in partially isolated subpopulations (called demes). Altruists (A's) take an action costing c that confers a benefit b on an individual randomly selected from the n members of the deme. (Payoffs are given in Table 1, and the model and notation are summarized in Table 2.) A's are bearers of a hypothetical "altruistic allele"; those without the allele (N's) do not behave altruistically. Reproduction is asexual. In the absence of reproductive leveling, individual fitness is identical to the payoffs in Table 1. For example, an A who interacts solely with A's will expect a number of offspring surviving to reproductive age that is $b - c$ greater than the fitness of an N who interacts only with N's.

Let $p_{ij} = 1$ if individual i in deme j is an A with $p_{ij} = 0$ otherwise. Let p_j be the fraction of deme j's membership that are A's; p and p' be the A-fraction of the metapopulation in a given and subsequent generation, respectively; and $\Delta p \equiv p' - p$. Then, following Price (*17*) and assuming the metapopulation size does not change, we can express the possible evolution of altruism as summarized by Δp as a between-deme effect plus a within-deme effect:

$$\Delta p = \mathrm{var}(p_j)\beta_G + \mathrm{E}\{\mathrm{var}(p_{ij})\}\beta_i \qquad (1)$$

The terms $\mathrm{var}(p_j)$ and $\mathrm{E}\{\mathrm{var}(p_{ij})\}$, are, respectively, the between-deme and within-deme genetic variance. (E{} indicates a weighted average over demes.) The coefficient β_G is the effect of variation in p_j on the average fitness of members of deme j (w_j); β_i is the effect of variation in p_{ij} (namely, switching from an N to an A) on the fitness of an individual in deme j (w_{ij}). A behavior is altruistic if adopting it lowers one's expected fitness while increasing the average fitness of one's deme (*18*). Given this definition, we are interested in the case where β_i is negative and β_G is positive.

Using Eq. 1, we see that whether altruism evolves ($\Delta p > 0$) depends on the outcome of a race in which the between-selection process promoting its spread [$\mathrm{var}(p_j)\beta_G$] competes with the within-selection process tending to eliminate it ($\mathrm{E}\{\mathrm{var}(p_{ij})\}\beta_i$). For the between-deme effect to exceed the within-deme effect (rearranging Eq. 1), it must be that

$$\frac{\mathrm{var}(p_j)}{\mathrm{E}\{\mathrm{var}(p_{ij})\}} > -\beta_i/\beta_G \qquad (2)$$

The left-hand side of this condition is a measure of positive assortment arising from the fact that if the fraction of A's in demes differ [that is, $\mathrm{var}(p_j)$ is positive], then A's are more likely than N's to interact with A's.

Because the within-deme benefits of altruism are randomly distributed, between-deme differences in the prevalence of A's [i.e., $\mathrm{var}(p_j) > 0$] is the only reason why A's are more likely than N's to interact with A's and thus to benefit mutually. But if A's are likely to benefit for this reason, they are also more likely to compete over deme-specific resources (*19*, *20*). I assume the most stringent form of local density-dependent constraints on reproductive output: Sites are saturated so that territorial expansion is required for deme growth. Thus, altruism can proliferate only by helping a deme to acquire more territory, not by any of the other ways that members of predominantly altruistic demes might produce more surviving offspring.

Selective group extinction. Selective extinction may allow the evolution of altruism if predominantly altruistic demes are more likely than other demes to survive between-deme contests and to colonize and repopulate the sites vacated by demes that fail (*21*). This process is captured by the term β_G, the size of which is determined by the frequency of contests, the fitness effects of surviving a contest, and the contribution of altruists to surviving.

In every generation with probability κ, each deme engages in a "contest." (A contest may be a

Table 1. Payoffs to within-deme interactions. Entries are the payoffs of the row individual when interacting with an individual whose type is given by the column head.

	Altruist	Not
Altruist (A)	$1 + b - c$	$1 - c$
Not (N)	$1 + b$	1

hostile encounter or an environmental challenge without direct deme interaction.) Demes that fail are eliminated, and surviving demes repopulate the vacated sites. Early human demes probably faced frequent intergroup, environmental, and other challenges resulting in occasional fatalities or territorial losses or gains [more closely resembling boundary skirmishes among chimpanzees (*22*) than this all-or-nothing deme-extinction scenario]. I show (*13*) that estimates of long-term fitness effects of continuous low-level losses or gains are equivalent to a complete extinction-repopulation scenario occurring infrequently.

Demes are the same size (normalized to 1), except that demes that have occupied the site of an eliminated deme are momentarily of size 2 (and eliminated demes are of size zero). The surviving deme divides, forming two daughter demes of equal size. Let the probability that the deme survives be λ. The size of deme j in the next generation is thus 1, 2, or 0 with probabilities $(1 - \kappa)$, $\kappa\lambda$, and $\kappa(1 - \lambda)$, respectively, so the expected size is $w_j = 1 - \kappa + 2\kappa\lambda$. The effect of the prevalence of A's on the expected size of the deme in the next generation (that is, $\beta_G \equiv dw_j/dp_j$) is the likelihood of a contest (κ), times the effect on deme size of surviving or not (*2*), times the effect of the prevalence of A's on the probability of a deme surviving should a contest occur (that is, $d\lambda/dp_j \equiv \lambda_A$); so $\beta_G = \kappa 2\lambda_A$. There is no way to estimate λ_A empirically, so I explore two alternative values (*13*): $\lambda_A = 1$ is derived from a model in which all-A and all-N demes (respectively) survive and fail with certainty should a contest occur; whereas if $\lambda_A = \frac{1}{2}$, an all-A deme survives with probability $\frac{3}{4}$ and an all-N deme survives with probability $\frac{1}{4}$.

Reproductive leveling. Distinctive human practices within groups also created a favorable niche for the evolution of altruism. Individual differences in size, health, behavior, and other influences on access to scarce resources are typically reflected in differences in reproductive success. Among some primates (*23*, *24*), and especially among humans, reproductive leveling attenuates this relation. Because altruists receive lower payoffs than other deme members (by the definition of altruism), they benefit from reproductive leveling, resulting in a reduction of the term β_i.

To see how this works, suppose an N were instead an A. In the absence of reproductive leveling, its fitness would be less by an amount c. But the individual would also have a $1/n$ chance of garnering the benefit b, which is distributed randomly to members of the group. Additionally, by increasing the chance of survival of the deme (in which case, like every member of the surviving deme, it will be doubled), it also contributes directly to its own fitness an amount equal to $1/n$ (i.e., the effect of the switch from N to A on p_j) times β_G (the effect of variations in p_j on the average fitness of the deme). Thus

$$\beta_i \equiv dw_{ij}/dp_{ij} = -c + b/n + \kappa 2\lambda_A/n \qquad (3)$$

Reproductive leveling can now be introduced by representing it as a convention, conformity to which is in the interest of each deme member (*25*). Let some portion of the payoffs initially acquired by an individual be distributed equally among all deme members. Reproductive leveling then takes the form of a proportional deduction at rate τ of each member's payoffs, the proceeds of which are distributed equally to all members of the deme. The effect is to reduce within-deme fitness differences between A's and N's from $-c$ to $-(1 - \tau)c$, so $\beta_i = -(1 - \tau)c + b/n + \kappa 2\lambda_A/n$.

Positive assortment and the evolution of altruism. Substituting these values for β_i and β_G in Eq. 1, we have

$$\Delta p = \mathrm{var}(p_j)\kappa 2\lambda_A - \mathrm{E}\{\mathrm{var}(p_{ij})\}\{(1 - \tau)c - (b + \kappa 2\lambda_A)/n\} \qquad (4)$$

We will assess this condition with genetic data from recent hunter-gatherer populations, using a commonly measured statistic from population genetics, the fraction of the total genetic variance at a locus that is between groups, also known as Wright's inbreeding coefficient (*26*): $F_{ST} \equiv \mathrm{var}(p_j)/[\mathrm{var}(p_j) + \mathrm{E}\{\mathrm{var}(p_{ij})\}]$. Using this definition, we rewrite Eqs. 2 and 4 and find that the A's share of the metapopulation will increase if

$$\frac{F_{ST}}{(1 - F_{ST})} > -\frac{\beta_i}{\beta_G} = \frac{(1 - \tau)c - b/n}{\kappa 2\lambda_A} - \frac{1}{n} \qquad (5)$$

If n is large, this is approximated by

$$\frac{F_{ST}}{(1 - F_{ST})} > \frac{(1 - \tau)c}{\kappa 2\lambda_A} \qquad (6)$$

Like Hamilton's rule for the evolution of altruism by inclusive fitness, this model thus yields a condition indicating the minimum degree of positive assortment necessary to allow altruism to proliferate. The left-hand term, like Hamilton's degree of relatedness (r), is a measure of positive assortment; but here assortment arises solely from between-deme differences in the prevalence of A's. The right-hand term in Eq. 6 is the ratio of individual costs to group-level benefits. We now ask if ancestral humans are likely to have lived under conditions such that Eqs. 5 or 6 would be satisfied. Table 3 is a summary of the main parameters and the estimated range of empirically plausible values.

Empirical estimates of F_{ST}. Wright [(*27*), p. 203] speculated that an equilibrium F_{ST} among human groups—namely, that which would balance the offsetting effects of migration and drift—might be about 0.02, a value that would preclude interdemic competition as an important evolutionary force. But most empirical estimates are considerably larger. The measures of genetic differentiation in Table 4 are from recent foraging populations whose population structure, geographical and linguistic proximity, and livelihood may resemble those of foraging bands of the late Pleistocene and early Holocene (about 150,000 to 10,000 years before the present). These estimates are based on genetic material, most of which was collected before the mid-1970s, and in most cases are averages over a large number of genetic systems and over F-statistics among a large number of subpopulations. A nested three-level hierarchy of measures of genetic differentiation is estimated, depending on the size of the subpopulation units (*13*): F_{DG} measures genetic differentiation among demes (D) in the same ethno-linguistic group (G), whereas F_{GT} and F_{DT}, respectively, measure differentiation among groups and demes in a metapopulation (T). If most competition is between demes across ethno-linguistic boundaries, then F_{DT} is the relevant statistic.

I think it is unlikely that Table 4 overestimates the relevant degree of genetic differentiation among early humans. First, extreme

Table 2. Summary of model and notation. b and c: benefits and costs to deme members; p_k: percent of deme k that are A's; and p: percent of metapopulation that are A's.

Notation	Eq. no.	Equation	Comment
Generic Price equation (PE)	1	$\Delta p = \mathrm{var}(p_j)\beta_G + \mathrm{E}\{\mathrm{var}(p_{ij})\}\beta_i$	Δp = between deme + within deme
Generic PE condition for A to increase	2	$\mathrm{var}(p_j)/\mathrm{E}\{\mathrm{var}(p_{ij})\} \equiv F_{ST}/(1-F_{ST}) > -\beta_i/\beta_G$	$F_{ST} \equiv$ between-deme var/total var
Effect of A on deme-average fitness (β_G)		$\beta_G \equiv dw_j/dp_j = \kappa(dw_j/d\lambda)(d\lambda/dp_j) = \kappa 2\lambda_A$	κ = probability of interdemic contest
Effect of A on individual fitness (β_i)		$\beta_i \equiv dw_{ij}/dp_{ij} = -(1-\tau)c + b/n + \kappa 2\lambda_A/n$	τ = extent of reproductive leveling
Condition for A's to increase (Price equation)	4	$\Delta p = \mathrm{var}(p_j)\kappa 2\lambda_A - \mathrm{E}\{\mathrm{var}(p_{ij})\}\{(1 - \tau)c - (b + \kappa 2\lambda_A)/n\}$	Δp = between–deme + within-deme effect
Condition for A's to increase	5	$F_{ST}/(1-F_{ST}) > -\beta_i/\beta_G = \{(1-\tau)c - b/n\}/\kappa 2\lambda_A - 1/n$	Larger F_{ST} favors A's.
Condition for A's to increase (if $n = \infty$)	6	$F_{ST}/(1 - F_{ST}) > (1 - \tau)c/\kappa 2\lambda_A$	> individual cost/deme benefit

climate variability during the late Pleistocene (fig. S3) probably induced frequent deme extinctions, population crashes, and subsequent growth, resulting in the colonization of new sites by small propagules. Natural experiments [e.g., with the plant *Silene dioica* (*28*)] suggest that the effect may be a considerable elevation of between-group genetic variance. Second, genetic differentiation among a subspecies of chimpanzees (*Pan troglodytes schweinfurthii*) whose spatial distribution and demographic history may resemble those of early humans (*29*) is substantially higher than the median of the estimates in Table 4 (F_{ST} = 0.102).

However, genetic differentiation at the locus of an allele that is expressed in an altruistic behavior may differ from that estimated for neutral loci (those not under selection) such as those in Table 4. First, an altruistic allele would be (by definition) under directional selection. This would be expected to reduce interdemic genetic differentiation at least in the very long run, because in the absence of offsetting effects, the frequency of the A's in the population will eventually go to zero. However, this tendency may not work over time scales relevant to human demes. Simulations (*13*) show that even for very strong selection against the A's and for plausible initial distributions of A's in demes, the F_{ST} rises for tens of generations. For moderate selection against the A's, the F_{ST} may rise for more than a hundred generations before falling. Because fission and extinction events that enhance interdemic variance are likely to be an order of magnitude more frequent than this, it appears that high levels of F_{ST} could persist indefinitely. Even with random fission (and relatively small demes), additional simulations (*25*) show that exceptionally strong directional selection against the A's (c = 0.1) is compatible with the indefinite maintenance of high levels of F_{ST}.

Second, altruists will sometimes be able exclude nonaltruists from their demes, resulting in what Eshel and Cavalli-Sforza called "selective assortment" (*30*, *31*). This is particularly common when demes fission, a process Hamilton (*32*) called "associative tribe splitting." Directed migration (*33*) will also enhance between-deme variance and reduce within-deme variance. Here, selective assortment is contingent on past behavior that is itself an observable expression of the altruistic allele. As a result, the only way an N can mimic the A's so as to evade their choosiness is to adopt the altruistic behavior itself and thus to bear its costs. Thus, the instability arising in the case of assortation by "green beards" (*34*) does not arise.

But there is nonetheless an impediment to selective assortment that is sometimes overlooked: Exclusion of N's is likely to be costly for the A's, whereas the associated benefits are shared by all deme members. However, it is not implausible that altruists would undertake some moderate level of N-exclusion as a contribution to the public good. There is ample ethnographic evidence (*11*) that foragers practice selective assortment when they ostracize or shun individuals who violate behavioral norms. Models and simulations (*35*) confirm that these practices can proliferate when rare and persist indefinitely in a plausible evolutionary dynamic. Moreover, it is readily shown (*13*) that a modest amount of selective assortment generates substantial levels of between-deme differences.

Within-deme selection. Although the effects of most forms of reproductive leveling cannot be estimated, the degree of within-deme resource sharing is known from empirical studies of the acquisition and consumption of nutrition among foragers (*13*). On this basis, I take $\tau = \frac{2}{3}$ as a plausible benchmark with $\frac{1}{3}$ an alternative value (*13*).

The appropriate value of n is the number of deme members of a breeding generation (about a third of the census size). The median band (census) size in the most comprehensive survey (*13*) is 19. Individual bands may have competed for survival, but it is likely that bands in coalition also engaged in contests. A plausible benchmark is that a deme is five bands, giving n = 32; I will also consider very large (strictly, infinite) demes.

Plausible values of c and b will depend on the particular altruistic behavior in question. For example, a warning call would have a different b and c than defending the community against hostile neighbors. To facilitate the exploration of a variety of altruistic behaviors, I present results for a given b = 0.05 and c varying from 0 to 0.08. (Eqs. 5 and 6 make it clear that for sizable demes, b is of little importance.)

Deme extinction. The extent of hostile group interactions during the late Pleistocene and early Holocene may be suggested by climatic data, hunter-gatherer demographics, archaeological evidence, and recent histories of foraging peoples, and is a matter of some debate [the evidence is reviewed in (*13*)].

We know from ice and deep-sea cores that average temperature during the late Pleistocene varied by as much as 8°C over periods of less than two centuries—the difference in average contemporary annual temperatures between Cape Town and Mombasa, 4000 km to the north (fig. S3). Mortal challenges resulting from climatic adversity must have been frequent, as well as from hostile interactions among groups migrating over unfamiliar terrain without established arrangements

Table 4. Genetic differentiation among 13 hunter-gatherer subpopulations (*13*). The median and mean values (respectively) are 0.076 and 0.081. The median and mean for the F_{DT} estimates are 0.081 and 0.093.

Population	Index	*F*
Indigenous circumpolar Eurasian populations	F_{DT}	0.076
Native Siberian populations	F_{DT}	0.170
Native Siberian populations	F_{DG}	0.114
!Kung demes (Southern Africa)	F_{DG}	0.007
Southern African groups	F_{GT}	0.075
Southern African demes (from 18 groups)	F_{DT}	0.081
Aboriginal Australians	F_{GT}	0.042
Kaiadilt-Lardiil groups (Australia)	F_{DT}	0.081
Asmat-Mappi (Lowland Western New Guinea):	F_{DT}	0.056
Mbuti (Central Africa)–San (Southern Africa)	F_{GT}	0.149
Aka (Central Africa between "villages" in the same group)	F_{DG}	0.042
Aka (between groups)	F_{GT}	0.057
Aka (between "villages" in all groups)	F_{DT}	0.097

Table 3. Parameter estimates. Benchmark values are in bold. Entries not in bold are alternative values (δ = 0.4 not used).

Determinant		Range explored	Comment/method of estimation (*13*)
Interdemic genetic differentiation	F_{ST}	0.007–0.170; **0.076**	Genetic markers (recent foragers)
Reproductive leveling	τ	**0.66,** 0.33	Food sharing (recent foragers)
Gains – losses from contests per generation	δ	**0.30**, (0.40)	Archaeological and ethnographic evidence
Per-generation probability of a decisive (2,0) contest	κ	= δ**/2**	Based on estimates of mortality in ongoing conflict
Effect of percent altruists on deme survival	λ_A	**½, 1**	Arbitrary (see Fig. 1)
Effective deme size (one-third of census size)	n	**32**, ∞	Coalition of 5 median-sized bands
Cost to altruist	c	**0.0** to **0.08**	Depends on behavior under consideration
Benefits to deme members (without a contest)	b	**0.05**	As immediately above

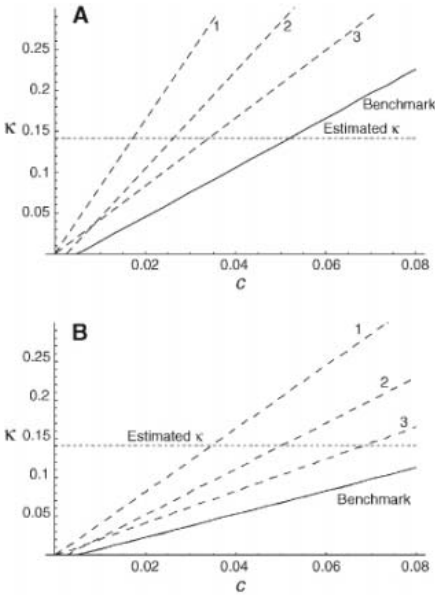

Fig. 1. Conditions for the evolution of altruism by selective extinction and reproductive leveling if $F = 0.076$. The solid lines are the benchmark values estimated in the text ($n = 32$, $\tau = 0.66$). Line 1: $n = \infty$, $\tau = 0.33$; line 2: $n = 32$, $\tau = 0.33$; line 3: $n = \infty$, $\tau = 0.66$. Points above each line give combinations of c and κ such that altruism would proliferate according to Eqs. 5 and 6. (**A**) $\lambda_A = ½$; and (**B**) $\lambda_A = 1$. For both panels, $b = 0.05$.

for peaceful coexistence. Frequent catastrophic mortality is the most plausible way to reconcile two facts about hunter-gatherer demography—namely, that human population grew extraordinarily slowly or not at all for the 100,000 years prior to 20,000 years before the present (*36*), yet models and data on hunter-gatherer demographics show that they are capable of growth rates exceeding 2% per annum (*37*).

A few archaeological sites from the late Pleistocene suggest that exceptionally lethal warfare took place and that violence intensified during periods of climatic adversity and resource stress (*13*). Deaths due to warfare constitute a substantial fraction of all deaths among foragers, averaging 13% on the basis of archaeological data (violent deaths, table S3) and 15% on the basis of ethnographic studies. This is much more than for Europe and the United States in the 20th century (less than 1% of male deaths). Territorial loss or gains due to warfare among a small sample of foraging groups averaged 16% per generation. Based on averages of three large samples from the ethnographic record (table S4), war was "rare" in only a fifth of the hunter-gatherer societies and "continuous" in a third.

I show (*13*) that the level of ongoing hostility indicated by these data would produce fitness effects equivalent to the extinction-repopulation scenario modeled above occurring every five to seven generations, the latter figure ignoring war casualties and considering only the demographic effects of territorial losses and gains. Neither estimate includes extinctions induced directly by climate change or other events unrelated to war. I use the smaller estimate of the frequency of conflicts ($\kappa = {}^1/_7$).

Discussion. The above estimates are subject to substantial error given that they are inferences about conditions occurring tens of thousands of years ago for which very little direct evidence is available. With this caveat in mind, suppose early humans' demographics and social practices resulted in genetic differentiation at the locus of an altruistic allele that was the magnitude of the median in Table 4 ($F = 0.076$). For the benchmark values of τ, n, and λ_A, the solid lines in Fig. 1 give the combinations of c and κ such that Eq. 5 is satisfied as an equality. More frequent contests or less costly forms of altruism (points above the line) allow altruism to proliferate. Dashed lines do the same for more stringent alternative parameter values. For example, for the estimated κ, if $c = 0.05$, altruism proliferates (for both values of λ_A) under the benchmark assumptions, but not for very large demes with limited reproductive leveling. Similar analysis for all of the data in Table 4 is presented in (*13*).

For many of the populations in Table 4 and for plausible parameter values, then, genetic differentiation is such that even very infrequent contests would have been sufficient to spread quite costly forms of altruism. Because the initial spread of altruism among humans could have been propelled by just a few of the vast number of late Pleistocene demes, the above data and reasoning suggest that selective deme extinction may be part of the account of the evolution of altruism. This is likely in the presence of appreciable levels of reproductive leveling (and not in its absence), suggesting an important role for culturally transmitted practices in creating a niche in which a genetic predisposition to behave altruistically might have evolved, and perhaps accounting for the distinctive aspects of human altruism not found in other species. Whether related processes of interdemic competition might support the evolution of cooperative behaviors in the absence of highly developed cultural transmission and cognitive capacities [as has recently been suggested for euosocial insects (*38*)] is an empirical question that remains to be addressed.

Nothing here implies that a genetic disposition favoring human altruism exists, or that cultural or other possible explanations of human altruism are of lesser importance. The evidence does suggest that if such a disposition exists, it may be the result of a gene-culture coevolutionary process in which, as Darwin wrote, group conflict played a key role.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5805/1569/DC1
SOM Text
Figs. S1 to S5
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References and Notes

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Present-Day Impact Cratering Rate and Contemporary Gully Activity on Mars

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The Mars Global Surveyor Mars Orbiter Camera has acquired data that establish the present-day impact cratering rate and document new deposits formed by downslope movement of material in mid-latitude gullies on Mars. Twenty impacts created craters 2 to 150 meters in diameter within an area of 21.5×10^6 square kilometers between May 1999 and March 2006. The values predicted by models that scale the lunar cratering rate to Mars are close to the observed rate, implying that surfaces devoid of craters are truly young and that as yet unrecognized processes of denudation must be operating. The new gully deposits, formed since August 1999, are light toned and exhibit attributes expected from emplacement aided by a fluid with the properties of liquid water: relatively long, extended, digitate distal and marginal branches, diversion around obstacles, and low relief. The observations suggest that liquid water flowed on the surface of Mars during the past decade.

The Mars Global Surveyor (MGS) spacecraft has just completed its ninth year (~4.8 Mars years) and third mission extension (*1*) acquiring scientific data from Mars' orbit. Extended missions have allowed the MGS and its Mars Orbiter Camera (MOC) (*2*) to make discoveries based on changes in observations over time and increased surface area coverage. We report two key findings of the MGS extended mission: measurement of the present-day impact cratering rate and formation of new deposits by downslope fluidized movement of material in mid-latitude gullies.

Present-day impact cratering rate. On 6 January 2006, a chance observation was made in a MOC wide-angle context frame acquired for a narrow-angle image. This 230-m/pixel image contained a dark spot with a 1-km diameter that had not been seen previously (Fig. 1A). In February, the MGS spacecraft was rotated to point the MOC narrow-angle camera at the new spot. A ~1.5-m/pixel image was obtained showing a fresh meteoritic impact site (Fig. 1B). The dark spot seen in the 230-m/pixel image is largely the product of atmospheric processes related to the interaction between the hypervelocity meteoroid and the atmosphere, combined with the shock wave from the actual impact, both of which mobilized dust on the surface at and around the site. Examination of other MOC and Mars Odyssey Thermal Emission Imaging System (THEMIS) images showed that the dark spot, and thus the impact, definitely formed after 12 November 2004, and may have formed after 13 April 2005 [supporting online material (SOM) text].

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From this initial effort, we began a campaign to find other recent crater sites in areas where similar small impacts may have darkened the surface over an area large enough to observe in 230-m/pixel images. In May and early June 1999, we had acquired full-resolution MOC red wide-angle images of the martian surface north of 55°S during the MOC geodesy campaign (*3*). To identify candidate new impacts, during January to March 2006 we acquired new red wide-angle images of three bright, dusty regions on Mars (Amazonis, Tharsis, and Arabia). As the data came in, they were map projected and compared with the 1999 data.

Thirty-nine candidate dark spots were identified in the study area of 21.5×10^6 km^2, and they were targeted by the MOC narrow-angle camera. Of the 39 spots, 20 were found to be the sites of impacts (Fig. 1, C and D) (SOM text). Because only the craters that created dark spots in high-albedo areas can be seen easily, we believe that this is an undermeasurement but areally representative of the number of impacts that occurred between May 1999 and March 2006. Some of the craters were found in the darker portions of Amazonis, Tharsis, and Arabia. Comparing the relative area of the darker regions to the brighter regions within our study locations suggests that undersampling was substantially less than a factor of two. Also, most of the formation dates constrained by the acquisition dates of other images (SOM text) occurred after the 2001 global dust event; it is possible that some dark spots were covered by dust fallout from those storms and thus were not visible in our 2006 images. Notwithstanding these caveats, these observations are a direct measurement of the present-day impact cratering flux on Mars.

Of the 20 impact events, 7 created multiple craters, mostly within a few tens of meters of each other. The craters observed ranged from just over 2 to 148 m in diameter. For the purposes of establishing a single-crater equivalent radius, the single-crater radii of the multiple crater events were combined by taking the cube root of the sum of the cubes of their radii. The size of the craters we observed were likely formed by meteoroids a few tens of centimeters to ~2 to 3 m in diameter (*4*).

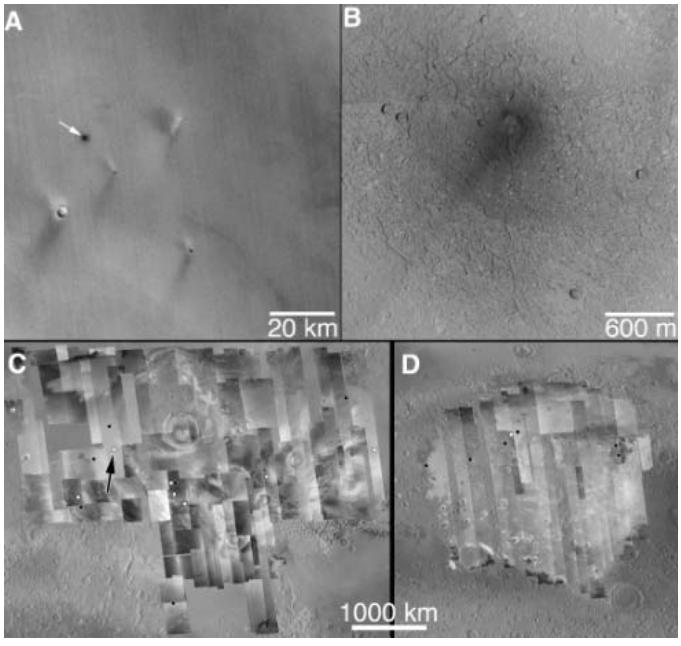

Fig. 1. (**A**) Dark spot (arrow) noticed in a MOC red wide-angle image acquired 6 January 2006 (subframe of MOC S14-00672). (**B**) Seen at higher resolution, the dark spot is the site of an impact that occurred after November 2004 (composite of subframes of MOC images S15-02128 and S16-01426, located near 14.0°N, 151.5°W; North is up). (**C**) Amazonis/Tharsis and (**D**) Arabia study areas. White dots represent sites where multiple craters were seen; black dots represent locations of single craters. Arrow in (C) indicates location of crater in (A) and (B). The rectangular strips are the MOC red wide-angle camera images obtained in January to March 2006, overlaid on a shaded relief map derived from MGS Mars Orbiter Laser Altimeter data and MOC red wide-angle images acquired in 1999.

Crater occurrence is not clustered spatially and does not correlate with altitude, although more multiple-crater sites are present in Amazonis and Tharsis than in Arabia. The diameter of each crater and the size of its associated blast zone (*5*) are unrelated, as are the blast zone diameter and altitude. Detailed examination of MOC and THEMIS images establishes intermediate dates (between 1999 and 2006) for the formation of many of the craters, indicating that they did not form at the same time. Indeed, the date that one of the craters formed can be constrained to a period of <40 days (SOM text). In another example, two craters that formed within a few hundred kilometers of each other occurred more than 5 months apart and were thus created by uncorrelated events (SOM text).

Most of the impact sites exhibit intricate albedo and ejecta patterns. Areas darker than their surroundings generally indicate locations of preferential dust removal, whereas lighter areas tend to be those at which light-toned subsurface material has been ejected by the crater (Fig. 2, A to D). Some of the craters show extensive rays, secondary impacts, and patterns that reflect the near-surface interactions of the impact event with the atmosphere (Fig. 2, E and F).

Our observations provide a means to validate theoretical models for the minimum size of primary craters owing to atmospheric filtering (during which objects ablate away before hitting the surface) (*6*–*8*). In addition, they provide evidence through attending phenomena (such as blast effects) that provide insight into the physical properties of the colliding objects (when and where in the atmosphere they break up into multiple objects) (*6*, *9*–*12*). For example, the compact distribution of craters in the multiple-crater sites suggests that the breakup occurred relatively close to the surface and with relatively low dispersive energy. The similarity in size of these craters and the general absence of substantive surface disruption between the craters suggests that the meteoroids disaggregated into a small number of similarly sized pieces. Our results appear to confirm models that the smallest craters formed by hypervelocity impact are likely to be a meter or more across (*6*) and suggest that micrometeoritic impact gardening or breakup of surface materials is a relatively minor component of martian erosion.

On airless bodies (the Moon being prototypical), impact craters are generally assumed to have accumulated monotonically with time over most of their histories; the longer the exposure, the larger the number of craters and the older the surface. Most investigators also assume that, since the formation of the lunar maria, the accumulation has been linear with time. Even on airless bodies such as the Moon, factors work against these assumptions: Throughout the bombardment history, secondary craters formed by material ejected by primary craters have also been added to the surfaces (*13*), and later impacts can affect earlier impact sites by either landing on top of them or by throwing ejecta over them (*14*, *15*). For solar system objects with atmospheres or active surface or geophysical processes, other factors can confound the simple model of accumulation by either filling in or covering craters or by removing the material in which the craters formed. Most martian surfaces have fewer and more widely spaced craters than do lunar surfaces (*16*), and this is attributed to the more extended geologic history of Mars, the surfaces of which have been formed throughout time.

A controversy arises when the details of the time scales as inferred from the martian cratering record are examined. The primary issue is that the paucity of craters implies that many processes (such as valley network formation, Tharsis central volcanism, and Marte Valles flows) have been active on Mars in the relatively recent past, somewhat at odds with other expectations based on geomorphic features and stratigraphic and cross-cutting relations. For example, a representative sample area within the 10,000 km^2 caldera of Arsia Mons (Fig. 3) displays a crater population that falls along isochrons (*17*) in the hundreds of millions of years. In comparison, essentially crater-free layered rock surfaces of many hundreds of square kilometers can be found in Candor Chasma. Acknowledging the likelihood of statistical variances when dealing with small areas, it is still possible to estimate from the isochrons the probability that a surface would remain free of craters after a specified duration of exposure. Using a conservative limit for the spatial resolution of MOC images of the area (the ability to see a crater of 10-m diameter), the Candor surface would fall on isochrons (*17*) indicating an age less than 100,000 years old. Given that these rocks are substantially older than that, as demonstrated by stratigraphic relations, they are likely exhumed (*18*). However, the absence of craters in such cases is disturbing, given the possible explanations: (i) The presently exposed rock materials do not retain craters, (ii) some active process has specifically removed or destroyed craters, (iii) a more generally

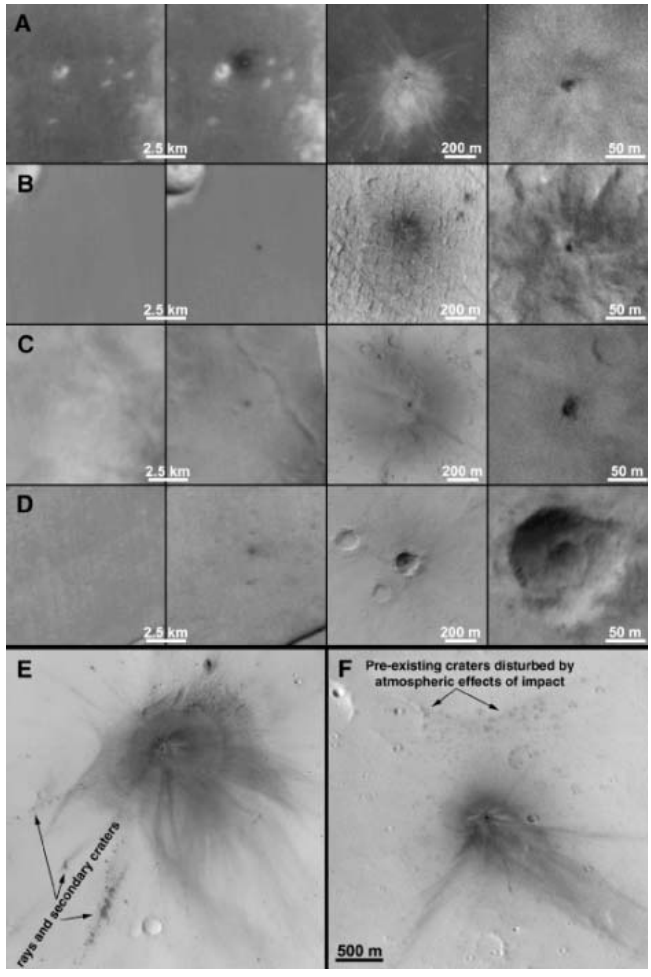

Fig. 2. Representative examples of recent impacts on Mars. The first column in (**A**) to (**D**) shows a "before" wide-angle view, the second column shows an "after" wide-angle view, the third column shows a portion of a subsequently targeted narrow-angle image, and the fourth column shows an enlargement of that narrow-angle image. Images in (**E**) and (**F**) show details of elaborate ejecta patterns, including rays and secondary craters, zones of enhanced dust removal, and areas affected by impact-generated atmospheric processes. In all cases, illumination is from the left and North is up. Image identification numbers can be found in the SOM text.

pervasive erosional process has affected the surface very recently, or (iv) the impact cratering story behind the development of the isochrons is incorrect. Because the rock retains steep escarpments on some individual layers and knobs of higher-standing, more resistant materials, (i) and (ii) are considered unlikely. A more generally active erosional process probably would have affected other adjacent areas, which does not appear to be the case, making explanation (iii) unlikely as well. Hence, our concern about explanation (iv), the cratering flux.

On one side of this issue are attempts to scale the lunar cratering history—determined by age dating of lunar rocks and measurements of the crater populations on the surfaces from which these rocks were derived—to Mars (taking into consideration, for example, the proximity of Mars to the asteroid belt, the higher velocity of objects orbiting the Sun at the distance of Earth and the Moon compared with those at Mars' distance, and the difference in gravitational acceleration) (*17*, *19*, *20*). On the other side are arguments that secondary cratering must be much more important than previously acknowledged, further positing that the spatial and temporal nonuniformity of such cratering must be responsible for the apparent discrepancies between crater counts and stratigraphic views (*21*, *22*).

The observed production of craters on Mars appears to be generally matched by the estimated isochrons (Fig. 4), potentially validating the assumptions made in generating these isochrons (*17*). However, some issues concerning the quality of the match should be noted. First, as the research that produced the isochrons evolved (*17*, *19*), the positions of the isochrons shifted by as much as a factor of 10 in time and/or crater numbers and a factor of 2 or more in diameter at the crater sizes discussed here. Also, the small number of craters observed, combined with diameter binning, means that the assignment of these values carries large statistical uncertainties. A line through our observations would not parallel the isochrons; the point representing the largest crater bin falls on the 100-year isochron, whereas the smallest bin falls well below the 1-year isochron (potentially a resolution effect). The 148-m diameter crater probably should be considered a 100-year crater, analogous to a 100-year flood (i.e., it has a 0.01 probability of occurring in any given year). Finally, the spacing of the isochrons strongly implies that the cratering rate is constant with time, which is a reasonable first-order assumption but one that is unlikely given the probable time history of production and temporal evolution of fragments generated by collisions within the solar system, which would imply an episodic cratering history.

Recent release of liquid water to the surface. Gullies (*23*) of relatively recent origin were first observed in early MGS MOC images (*24*). When their discovery was announced, they attracted considerable attention. Questions immediately posed included: Could the gullies be evidence that liquid water flowed on the surface recently? Could some gullies still be active today? Could evidence for the release of water be found by simply monitoring the gullies with orbiting cameras capable of sufficient spatial resolution (better than ~6 m/pixel) over the coming decades?

Most of the tens of thousands of gullies identified to date occur on slopes in craters, pits, and other depressions at latitudes ≥30°; a few exceptions occur at latitudes of 27° to 30° (*24*). Although some are straight, many gully channels are banked, some are sinuous, some meander, and most originate a few hundred meters below the local surface (*25*, *26*). In some cases, gully aprons exhibit multiple distributary channels or dozens to hundreds of individual flow lobes. The majority of gullies have alcoves that formed upslope by undermining, collapse, and mass movement, occasionally with contributory networks of small channels feeding the main channel (*24*).

The geomorphic expressions of the gullies suggest that the rheologic properties of the material that moved through them mimicked those of a fluid with the properties of liquid water or water-lubricated debris flows (*24*, *27*), with the fluid coming from groundwater (*25*, *26*, *28*, *29*), melting ground ice (*30*), or snowpacks (*31*, *32*). Gullies occur over a wide range of settings, mostly far from volcanic regions and possible endogenic hydrothermal sources. Alternative hypotheses for their origin center on the release of subsurface CO_2 (*33*, *34*) [which is unlikely owing to the difficulty in burying highly volatile CO_2 (*35*)] and formation by dry, granular flow (*36*).

Gullies appear to be geologically young features; estimates of their age center on their stratigraphic and geomorphic youth and their lack of superposed craters (*24*). Some investigators have speculated that gullies could not form under present climate conditions (*30*, *32*), but a more recent analysis calculated that the measured run-out distances of the gully channel and apron complexes are consistent with the flow of pure water under present atmospheric pressure and temperature conditions (*37*).

To look for changes that might indicate present-day fluid flow in gully channels, we repeatedly imaged thousands of gullies at hundreds of sites since 2000. This effort led to documentation of two sites at which new, light-toned flows formed since MOC first imaged the sites in 1999 and 2001. In the first example (Fig. 5, top), the floor and banks of a gully on the northwest wall of a crater in Terra Sirenum changed between December 2001 and when it was next imaged in April 2005 (MOC image S05-

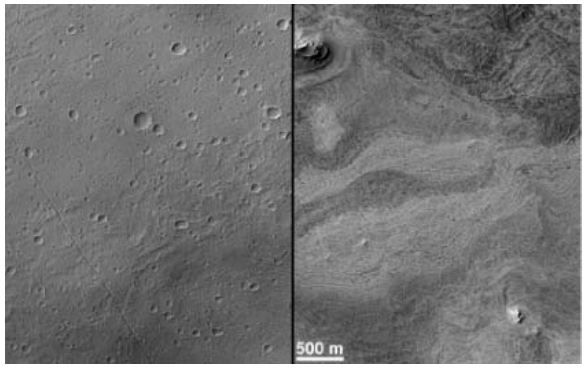

Fig. 3. Comparison of cratered surfaces (**left**) within the summit caldera of Arsia Mons (MOC E03-00354) and the layered materials (**right**) within Candor Chasma (MOC M02-00343). The images occur at similar latitude and similar solar incidence conditions; the Arsia Mons image is located near 9.0°S, 120.7°W, and was acquired near L_s 141° and solar incidence angle of 45.5°; the Candor Chasma image is located near 6.1°S, 75.7°W, near L_s 151° and solar incidence angle of 42.8°. Both images were acquired at 6 m/pixel scale; North is toward the top and upper right. L_s, the longitude of the Sun, is a measure of the position of Mars in its orbit of the Sun, relative to a fixed celestial coordinate system.

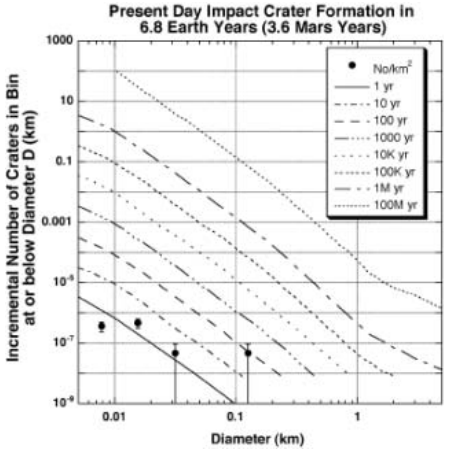

Fig. 4. Incremental size frequency relation for present-day impact cratering on Mars, compared with theoretical isochrons developed by Hartmann (*17*). Error bars show means ± 1 SD.

01463). A distinct light-toned flow (≤20% brighter than surrounding surfaces) appeared in the channel. Light-toned material, and adjacent surfaces, associated with other gullies on the north wall of the crater appear unchanged in a series of images (Fig. 6), indicating that the new brightening in the gully on the northwest wall is neither an illumination effect nor the result of differential eolian dust deposition or erosion. These materials, which resemble the new flow, suggest that this crater was the site of similar changes in the recent past.

In the second example (Fig. 5, bottom), the change occurred in a crater in the Centauri Montes region that has deeply incised gullies on its north wall (not shown in Fig. 5), and narrow, poorly seen (owing to low solar incidence angles) gullies on its southern wall (Fig. 5). The change occurred among the narrow gullies on the southern wall. Similar to the first example, a light-toned material flowed down the slope and formed a deposit. This surface was first imaged by MOC in August 1999. A portion of the bright deposit was first evident in February 2004 in MOC image R14-02285.

In addition to similar brightness values, the new light-toned deposits have relatively long, extended, digitate distal and marginal branches, they divert around obstacles, and they have relatively low relief (steep flow margins are absent). These attributes suggest a very fluid material (i.e., with the ability to divert around low-relief obstacles) that thins while flowing and buds easily into numerous branches; it also, in seeming contradiction, moves slowly (not able to over-top the low obstacles) down relatively steep slopes (photogrammetry indicates the slopes are between 20° and 30°). Such characteristics, plus the light tone, are consistent with the concept of flow of fluidized material through martian gullies to their aprons, periodically initiated and fed by the collapse of an ice-impregnated rock dam creating a brief, low-volume debris flow initially charged with liquid but in which ongoing freezing at both the top and bottom surfaces, bed infiltration, and incorporation of slope sediment and debris increases viscosity, which inhibits downslope and runout motion (*24*). If the deposits were created by a water-bearing fluid that flowed down these slopes, then they might contain ice, frost, or precipitates. Because the materials have retained their light tone over periods in excess of a martian year, and given the instability of water ice at these latitudes, the light tone may reflect replenishment of surface frost by exhalations from within the body of the deposit, ellutriation of fine-grained sediment, or precipitation of salts.

An alternative interpretation for these features is that they formed by downslope movement of dry dust. Slope streaks formed by mass movement of unconsolidated dust are common elsewhere on Mars (*38*, *39*). They have been observed to form during the course of the MGS mission, and some display attributes (including diversion around obstacles) that are reminiscent of the product of a flowing liquid (*39*). The majority of slope streaks are dark, but light-toned examples have also been found, often associated with or in the same areas as dark streaks. In our experience with the acquisition and analysis of >96,000 MOC narrow-angle camera images, we have not seen slope streaks, old or new, light or dark, on any gully-bearing mid-latitude slope, and none occurs in the two craters where the new gully deposits are found. Slope streaks most commonly occur in regions so thickly mantled with dust that the mantle's presence is obvious in MOC narrow angle images; these are most common in the dust-mantled regions of Tharsis, Arabia, Amazonis, and Elysium (*39*). Experiences ranging from observation of rover wheel tracks at the Mars Pathfinder and Mars Exploration Rover Spirit sites to the recognition of fresh impact crater sites described above suggest that disruption of a dusty surface usually results in darkening, not lightening, of that surface. Related to that experience, although hundreds of newly formed dark slope streaks have been found by repeatedly imaging with MOC areas known to display slope streaks, no newly

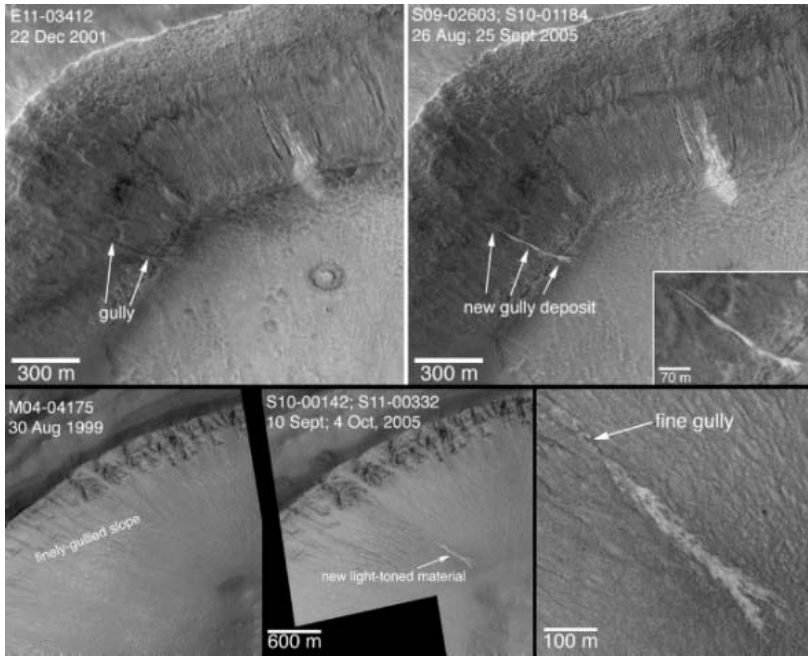

Fig. 5. (**Top**) Light-toned material deposited in a martian south mid-latitude gully between December 2001 and April 2005. The images shown here were acquired at about the same time of year (E11-03412 at L_s 295.2°; S09-02603 at L_s 276.0°; S10-01184 at L_s 295.0°). Note the digitate apron at the end of the gully in the inset at lower right. The gullies occur in a crater in Terra Sirenum near 36.5°S, 161.8°W; North is up. (**Bottom**) Light-toned material deposited on southwest wall of a crater in the Centauri Montes region near 38.7°S, 263.3°W. The material was transported through a fine gully channel and the deposit has a digitate terminus. The feature was not present when the crater was first imaged in August 1999. An image obtained in February 2004 (R14-02285) showed a portion of the bright deposit, indicating that it had formed sometime between August 1999 and February 2004. North is down and sunlight is from the lower right in these images.

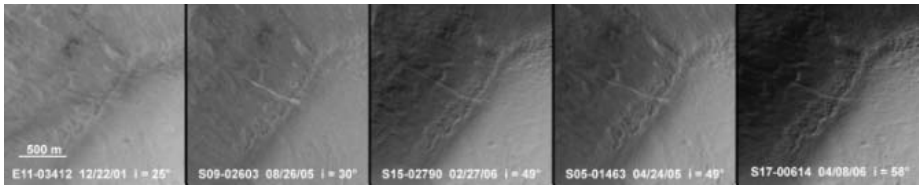

Fig. 6. New gully deposit at different illumination angles (i = solar incidence angle). The leftmost image was obtained before new deposit was emplaced, the others were taken after deposit was emplaced.

formed light-toned streaks have been observed. Indeed, where light and dark slope streaks occur together, the dark streaks always superpose the light streaks, and the newly formed streaks are always dark. The apparent brightening with time of dark slope streaks and adjacent light slope streaks suggests that light streaks might be formed from dark streaks over time.

Conclusions. The present-day martian cratering rate, as determined by direct observations of craters formed since 1999, is gradual and cumulative, and predicted values based on the scaling of lunar cratering to Mars are consistent with the observed rate. An alternative idea that most small craters are secondary craters that would form clustered in time does not describe present-day cratering. Attempts to use impact crater abundances to age-date martian surfaces are constrained by the evidence that such surfaces may not have retained all the craters formed and hence the crater ages apply mostly to the processes of martian erosion and denudation and not necessarily to the ages of the underlying rock units. In this regard, the paucity of craters on some important surfaces (such as the layered rock exposures in west Candor Chasma) and the determined impact rate, imply that these surfaces are truly youthful but further imply that there have been processes of denudation at work on Mars in the recent past for which we have yet to recognize other evidence.

Light-toned deposits that have formed since 1999 and 2001 at two gully sites in the martian southern hemisphere display characteristics highly suggestive of emplacement by fluidized flow. Their properties and geomorphic settings suggest that the fluid was water, consistent in spirit, if not in detail, with quantitative models suggesting that it is possible for liquid water to exist beneath the ground and come to the surface under modern martian conditions (*28*, *29*, *37*). As with many discoveries, the possibility that liquid water may be coming to the surface of Mars today poses many questions: Where is the water coming from? How is it being maintained in liquid form given the present and most likely past environments? How widespread is the water? Can it be used as a resource in further Mars exploration? Finally, has it acted as an agent to promote or sustain a martian biosphere?

References and Notes

1. MGS reached Mars in September 1997. Its primary mission, lasting one Mars year, began in March 1999. The first extended mission began in February 2001 and covered an additional Mars year. Since that time, the mission has been extended to cover a third and, currently, a fourth martian year. Because the MOC narrow-angle camera has a field of view of only 3 km, and the combination of onboard computer space and downlink capabilities limit the number of images acquired during a given Mars year, the camera has only imaged about 5.2% of the martian surface through October 2006.
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4. A simple estimate of the impact parameters can be made by calculating the energy of the impact. Such calculations are often heavy on assumptions. Assuming most of the energy goes into excavating the observed pits, the energy is proportional to the work done against martian gravity, lifting the volume of rock up out of the hole and piling it up adjacent to the hole. For our calculations, we assumed that the craters are roughly hemispherical, that the impact velocity was equivalent to the escape velocity (~5 km/s), and that the target density was 3 g/cm^3. For such assumptions, about 260 m^3 with a mass of 785,000 kg would be excavated to form a crater with a 10-m diameter. It would take about 13 MJ to lift this mass out of the crater, and for a density of 3.5 g/cm^3 (typical of chondrite meteorites), the object hitting the ground was probably about 10 cm across, with a mass around 1 kg. The largest crater seen (148-m diameter) was probably made by an object a couple of meters across, with a mass close to 50,000 kg. The smallest craters seen, about 2 m across, are probably close to the smallest that can be formed, given that the object would be so small that it would lose an appreciable portion of its total mass owing to ablation during passage through the atmosphere, and it would also experience significant deceleration.
5. For convenience and brevity, we use the term "blast zone" to cover all of the atmospheric effects associated with the impact, including the interaction with the surface of the shock wave accompanying the penetration of the atmosphere by the meteoroid, the centrifugal shock wave generated by the actual impact, the centrifugal overpressure wave trailing the shock wave, the centripetal backflow of atmosphere after the initial outflow, turbulence created by these flows, and airflow and turbulence induced by ejecta moving through the atmosphere.
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16. The density of craters on Mars and the Moon is a strong function of crater size and planetary geography. The lunar highlands have a high density of large craters (>50 km), but such high densities of large craters are quite rare on Mars. The mare surfaces have far fewer craters of such size but have numerous craters <1 km in diameter. Many surfaces on Mars are devoid of kilometer-scale craters.
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Figs. S1 to S4
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A Brown Dwarf Mass Donor in an Accreting Binary

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A long-standing and unverified prediction of binary star evolution theory is the existence of a population of white dwarfs accreting from substellar donor stars. Such systems ought to be common, but the difficulty of finding them, combined with the challenge of detecting the donor against the light from accretion, means that no donor star to date has a measured mass below the hydrogen burning limit. We applied a technique that allowed us to reliably measure the mass of the unseen donor star in eclipsing systems. We were able to identify a brown dwarf donor star, with a mass of 0.052 ± 0.002 solar mass. The relatively high mass of the donor star for its orbital period suggests that current evolutionary models may underestimate the radii of brown dwarfs.

The theory of binary star evolution invokes core astrophysics, including stellar models, magnetic braking, and gravitational radiation. Because a large fraction of all stars are found in binaries (*1*) and because the predictions of binary evolution theory describe some of the most exotic objects in our universe, including the likely progenitors of short γ-ray bursts (*2*) and type Ia supernovae (*3*) and how they may evolve with time, the study of binary star evolution has wide-ranging impact throughout astronomy and cosmology. It is therefore a cause of serious concern that the predictions of binary star evolution theory are, in some cases, dramatically out of line with observations. A prime example is the apparent lack of brown dwarf donor stars among the binaries known as cataclysmic variables (CVs). CVs are short-period [typically, with an orbital period (P_{orb}) of less than 1 day] binaries containing a white dwarf primary star and a low-mass donor star. The donor star is so close to the white dwarf that it is tidally distorted and fills a critical surface known as the Roche lobe, which determines the maximum extent of a star in a close binary. The secular evolution of CVs is driven by angular momentum loss due to gravitational radiation, magnetic braking of the donor star, and perhaps circumbinary discs (*4*). The removal of angular momentum from the binary drives mass transfer from the donor star to the white dwarf, via an accretion disc. The donor shrinks as it loses mass, causing the orbital period to decrease. This continues until the donor's mass drops below the hydrogen burning limit, at which point the donor star becomes a brown dwarf. The resulting changes in the donor's internal structure mean that it now expands in response to mass loss, causing the orbital period to increase (*5*). Thus, CVs are expected to show a minimum orbital period, and CVs that have evolved past the period minimum (post–period minimum systems) should possess brown dwarf donor stars. Theoretical studies (*6*, *7*) predict that around 70% of the current CV population have evolved past the orbital period minimum. However, despite extensive observational effort (*8*–*15*), not one of the ~1600 known CVs has a donor that has been unambiguously shown to be substellar (*8*).

Although there has been speculation that the rate of angular momentum loss is so low that systems may not have had time to reach their minimum period (*16*) or that the rate is enhanced so greatly by circumbinary discs that the donor is rapidly devoured (*17*), it may be that the observed lack of post–period minimum systems is a result of selection effects. Post–period minimum systems will have low mass transfer rates and will consequently be very faint. They may also lack the frequent outbursts that aid in identifying their younger counterparts (*18*). Even if post–period minimum systems do form part of the known CV population, direct detection of the donor star is extremely difficult against the background of the relatively bright white dwarf and accretion disc (*8*).

Recent developments have allowed these problems to be overcome. The Sloan Digital Sky Survey (SDSS) (*19*–*23*) detects much fainter objects than previous surveys, and because objects are selected on the basis of their spectra, CVs need not show outbursts to be included. The SDSS sample could therefore contain a large number of post–period minimum systems. Although direct detection of the donor star in these systems remains a challenge, it is possible to measure the mass and radius of the donor in eclipsing CVs. By fitting a simple physical model [see supporting online material (SOM) for details] to the eclipse light curve, it is possible to obtain a full solution of the geometrical and physical parameters of the binary, and in particular the masses of the white dwarf and donor (*24, 25*). Only three assumptions are made: that the matter transferred between the donor and the white dwarf follows a ballistic trajectory until it strikes the outer edge of the accretion disc; that the white dwarf follows a theoretical mass/radius relation; and that the donor fills its Roche lobe.

We applied this method to the short-period CV SDSS 103533.03+055158.4 (hereafter SDSS 1035). After discovery within the SDSS (*23*), our own follow-up Very Large Telescope spectroscopy (*26*) found the system to be eclipsing. We obtained high–time-resolution photometry of eight eclipses between 4 and 8 March 2006, using Ultracam on the 4.2-m William Herschel Telescope. Ultracam provides simultaneous photometry in the Sloan *u′g′r′* color filters with minimal dead time between exposures. Mid-eclipse times were calculated by averaging the white dwarf ingress and egress times, which are given by the minimum and maximum of the light curve derivative, respectively (*25*). The orbital ephemeris was found with a linear least-squares fit to the times of mid-eclipse, giving an orbital period of 82.0896 ± 0.0003 min. The eight eclipse light curves were phased according to our ephemeris, averaged, and then binned by five data points to produce an average light curve for each band (Fig. 1). Sharp steps in the light curves represent the ingress and egress of the white dwarf behind the donor. The white dwarf eclipse is symmetric around binary phase 0, with ingress and egress near phases –0.02 and 0.02, respectively. Also visible is the eclipse of the bright spot, where the gas stream hits the outer edge of the accretion disc. Bright spot ingress is visible near phase 0.01, with egress near phase 0.08. The presence of a bright spot confirms ongoing accretion, validating our assumption that the donor fills its Roche lobe. The average light curves in each band were fitted separately with a geometric model including a limb-darkened white dwarf and a bright spot modeled as a linear strip passing through the intersection of the gas stream and accretion disc (full details are contained in the SOM). The model results are combined with a theoretical white dwarf mass/radius relation to obtain a full solution for the binary parameters (Table 1).

The most important result is the donor's mass, $M_c = 0.052 \pm 0.002$ solar mass ($M_\odot$). This is comfortably below the hydrogen burning limit of around ~0.072 $M_\odot$ for solar metallicities (*27*), making the donor star in SDSS 1035 a confirmed brown dwarf in a CV; only one other is known in any accreting binary system (*28*). This discovery supports a fundamental and long-standing prediction of binary evolution theory that a population of post–period minimum CVs exists, thus refuting claims that binary evolution may be too slow for such systems to form (*16*). It also demonstrates that the

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SDSS CV survey is sensitive to post–period minimum systems; the spectroscopic properties of SDSS 1035 are not unusual for the short-period CVs found within the SDSS (*23*), and therefore, if the population synthesis models (*6*, *7*) are correct, the SDSS CV sample should contain large numbers of post–period minimum systems.

It is possible, though unlikely, that SDSS 1035 could have formed directly from a detached white dwarf/brown dwarf binary similar to WD0137-349 (*29*). The progenitors of such systems are solar-type stars with brown dwarf companions at separations of a few astronomical units (*30*); such binaries fall within the "brown dwarf desert" and are very rare (*31*), and so only a small percentage of CVs should form from binaries such as WD0137-349 (*29*). It is therefore much more likely that SDSS 1035 is indeed a post–period minimum CV. Even if SDSS 1035 formed from a white dwarf/brown dwarf binary, its existence shows that an accreting white dwarf/brown dwarf binary is a viable configuration. Because the secular evolution of CVs moves them toward this configuration, this makes the existence of post–period minimum CVs highly probable.

The white dwarf temperature, derived from the colors of the white dwarf eclipse (see the SOM), can be used to determine the long-term average of the mass transfer rate (*32*). We find a mass transfer rate of $(10 \pm 2) \times 10^{-12}\ M_{\odot}\ \mathrm{year}^{-1}$, which is in line with the predictions from gravitational radiation but inconsistent with predictions that include a circumbinary disc, in which the mass transfer rate is increased to $80 \times 10^{-12}\ M_{\odot}\ \mathrm{year}^{-1}$. Increased angular momentum loss due to circumbinary discs is invoked to explain many problems in binary evolution, including the discrepancy between the observed and predicted values of the minimum orbital period for CVs and the apparent lack of large numbers of post–period minimum systems (*4*, *17*). The low inferred mass transfer rate in SDSS 1035, however, argues against models including circumbinary discs to explain these discrepancies.

Table 1. Derived parameters of SDSS 1035. $R_{\odot}$, solar radius.

Mass ratio q	0.055 ± 0.002
Inclination i	83.1° ± 0.2°
Orbital separation a	0.622 ± 0.003 $R_{\odot}$
White dwarf mass M_w	0.94 ± 0.01 $M_{\odot}$
White dwarf radius R_w	0.0087 ± 0.0001 $R_{\odot}$
White dwarf temperature T^{eff}_w	10,100 ± 200 K
Donor star mass M_c	0.052 ± 0.002 $M_{\odot}$
Donor star radius R_c	0.108 ± 0.003 $R_{\odot}$
Disc radius R_d/a	0.362 ± 0.003

A comparison of the donor mass in SDSS 1035 to current evolutionary models (*4*) is shown in Fig. 2. We can see that the mass of the donor in SDSS 1035 is inconsistent with models where gravitational radiation is the sole source of angular momentum loss. The donor mass is consistent with models including a circumbinary disc, but these models are ruled out by the inferred mass transfer rate. The discrepancy between observed and predicted masses is probably not due to the rapid rotation and/or distortion of the donor (*33*) but might be due to irradiation from the white dwarf or to nuclear evolution of the progenitor star (*34*). Alternatively, the source of the discrepancy may lie with current stellar models, which are based on an up-to-date equation of state specifically calculated for very-low-mass stars, brown dwarfs, and giant planets (*35*). For the donor star in SDSS 1035 to fill its Roche lobe implies that the radius must be larger than predicted by ~10%. If current models do underestimate the radii of brown dwarfs, this implies that the inferred ages and masses of isolated brown dwarfs are in error. Additional theoretical work will be necessary to determine whether any or

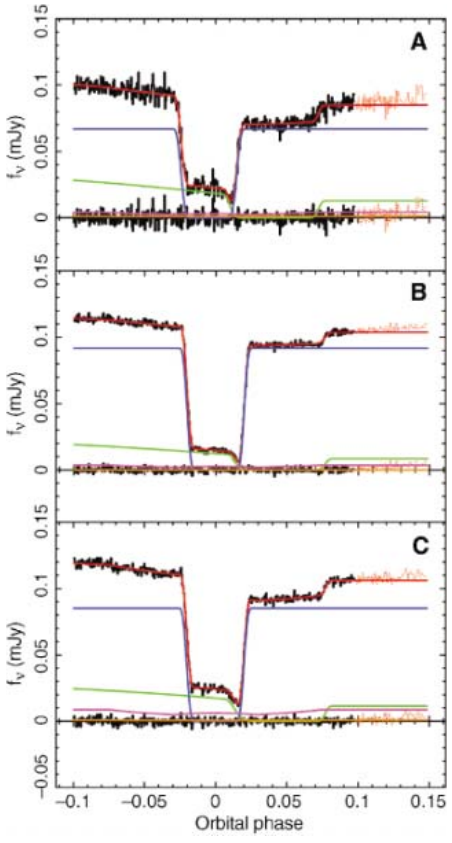

Fig. 1. Eclipse light curves and model fits for SDSS 1035. **(A)** The phase-folded *u*′ light curve. **(B)** The phase-folded *g*′ light curve. **(C)** The phase-folded *r*′ light curve. Each light curve is fitted separately using the model described in the SOM. The data (black) are shown with the fit (red) overlaid and the residuals plotted below (black). Also shown are the separate light curves of the white dwarf (blue), bright spot (green), accretion disc (purple), and donor star (orange). Data points excluded from the fit are shown in red.

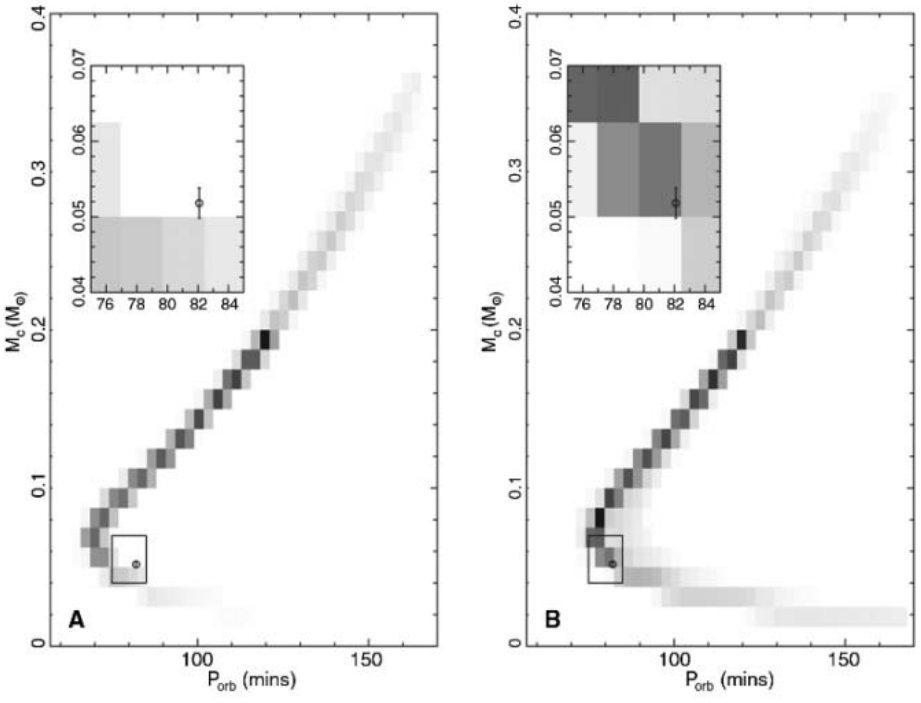

Fig. 2. Normalized probability distribution functions (PDFs) of the present-day CV population in the (M_c, P_{orb}) plane [adapted from (*4*)]. **(A)** Evolutionary tracks with angular momentum loss driven by gravitational radiation. **(B)** Evolutionary tracks with additional angular momentum loss from a circumbinary disc. The present-day CV population was obtained by weighting the contribution of each system to the PDF according to the accretion luminosity, as $L_{acc}^{1.5}$. In each panel an inset is displayed, showing the location of SDSS 1035 in the (M_c, P_{orb}) plane.

all of these ideas are sufficient to explain the discrepancy between the observed and predicted mass and radius presented here.

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Deep Mixing of ^{3}He: Reconciling Big Bang and Stellar Nucleosynthesis

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Low-mass stars, ~1 to 2 solar masses, near the Main Sequence are efficient at producing the helium isotope ^{3}He, which they mix into the convective envelope on the giant branch and should distribute into the Galaxy by way of envelope loss. This process is so efficient that it is difficult to reconcile the low observed cosmic abundance of ^{3}He with the predictions of both stellar and Big Bang nucleosynthesis. Here we find, by modeling a red giant with a fully three-dimensional hydrodynamic code and a full nucleosynthetic network, that mixing arises in the supposedly stable and radiative zone between the hydrogen-burning shell and the base of the convective envelope. This mixing is due to Rayleigh-Taylor instability within a zone just above the hydrogen-burning shell, where a nuclear reaction lowers the mean molecular weight slightly. Thus, we are able to remove the threat that ^{3}He production in low-mass stars poses to the Big Bang nucleosynthesis of ^{3}He.

The standard evolution of a low-mass star (Fig. 1) takes it from a short-lived pre–Main-Sequence (PMS) state, in which it contracts and heats up but has not yet become hot enough to burn its nuclear fuel, to the long-lived MS state in which slow, steady nuclear reactions keep the star in thermal equilibrium. After several gigayears (but depending strongly on mass), the nuclear fuel is exhausted at and near the center, the star becomes cooler, larger, and more luminous, and it starts to climb the red giant branch (RGB). Its outer layers become turbulent and convective, and this surface convection zone (SCZ) penetrates deeply into the star, but the SCZ is forced to retreat again as the fuel-exhausted core, surrounded by a thin, hot nuclear-burning shell, advances outward. During the growing phase, the SCZ dredges up and homogenizes material that, at the earlier MS phase, was processed by nuclear reactions in the interior.

Along the MS, stars burn hydrogen in their cores by a combination of the proton-proton (pp) chain (in which four protons unite to form a ^{4}He nucleus) and the CNO tri-cycle (in which the same process is catalyzed by carbon, nitrogen, and oxygen). The former is the more important in low-mass stars, $\leq 1\ M_\odot$, and the latter in more massive stars. However, even in the more massive stars there is still a shell, somewhat outside the main energy-producing region, where the pp chain partially operates, burning H to ^{3}He but not beyond.

Because the pp chain is less sensitive to temperature than the CNO cycle, cores of low-mass stars are free of convection, but convective cores develop in higher-mass stars because CNO energy production is too temperature sensitive for radiation to stably transport the energy. Above ~2 $M_\odot$ this convective core is large

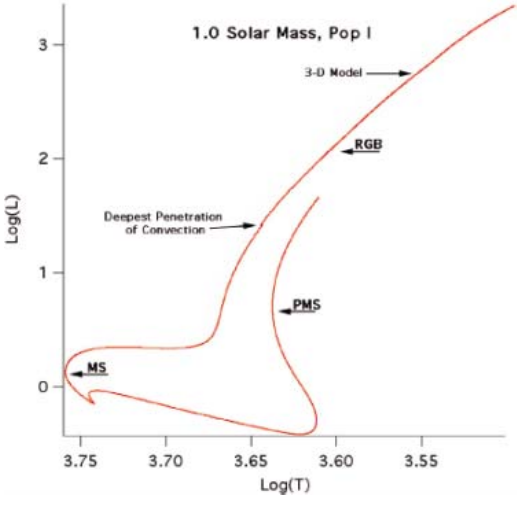

Fig. 1. Evolution of a low-mass Pop I star in a luminosity-temperature diagram. The model was computed in 1D, that is, spherical symmetry was assumed, using the code of (*20*, *21*) with updated equation of state, opacity, and nuclear reaction rates (*22*). Surface temperature is in kelvins, luminosity in solar units.

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enough that the ^{3}He produced is convected into the center of the star and burnt there. In stars of lower mass, however, ^{3}He accumulates (*1*) in a broad zone outside the main energy-producing region (Fig. 2A). ^{3}He is enriched above its assumed initial value [2×10^{-4} by mass (*2*), the same as its surface value in this plot] in a broad peak extending over nearly half the mass (as well as about half the radius) of the star. The maximum ^{3}He abundance in this peak is larger than the initial value by a factor of ~18.

On the lower part of the RGB (Fig. 1), a large SCZ develops, which mixes and homogenizes the outer ~0.7 $M_\odot$ (Fig. 2B). The surface ^{3}He abundance is raised from the initial value of 2×10^{-4} to ~1.6×10^{-3}, that is, by a factor of ~8.

As the star climbs the RGB beyond the point (Fig. 1) where the SCZ penetrates most deeply, the SCZ is diminished by (i) nuclear burning below its base, in a zone that marches outward, and (ii) stellar-wind mass loss from its surface. The evidence for the latter is that the next long-lived stage after the RGB is the horizontal branch (HB), and HB stars appear to have masses that are typically 0.5 to 0.6 $M_\odot$, substantially less than the masses of stars capable of evolving to the RGB in less than a Hubble time (*3*, *4*). Process (ii) leads to enrichment of the interstellar medium (ISM) in ^{3}He (*5*–*7*).

Yet the ISM's abundance of ^{3}He, at ~5×10^{-5} by mass, is little different from that predicted by Big Bang nucleosynthesis. This is a major problem (*8*, *9*): Either the Big Bang value is too high, or the evolution of low-mass stars is wrong.

Here, we identify a mechanism by which low-mass stars destroy (on the RGB) the ^{3}He that they produced during their MS evolution. Although we illustrate this with a star like the Sun, regarding both mass and initial composition, we emphasize that exactly the same applies to low-mass, metal-poor stars [Population II (Pop II)], which may have been more important than metal-rich stars [Population I (Pop I)] like the Sun throughout the earlier part of Galactic history in determining the ^{3}He abundance of the interstellar medium. The process is largely independent of mass provided it is fairly low: 1 to 2 $M_\odot$ for Pop I and 0.8 to 1.6 $M_\odot$ for Pop II.

Once the SCZ has reached its deepest extent, part way up from the base of the RGB, it retreats, and it can be expected to leave behind a region of uniform composition with ^{3}He enhanced (Fig. 2B). This region is stable to convection according to the usual criterion that the temperature gradient should be subadiabatic and is quite extensive in radius, although small in mass. The H-burning front moves outward into the stable region, but preceding the H-burning region proper is a narrow region, usually thought unimportant, in which the ^{3}He burns. The reaction that mainly consumes it is ^{3}He (^{3}He, 2p)^{4}He, which is an unusual reaction in stellar terms because it lowers the mean molecular weight: two nuclei become three nuclei, and the mean mass per nucleus decreases from 3 to 2. Because the molecular weight (μ) is the mean mass per nucleus, but including also the much larger abundances of ^{1}H and ^{4}He that are already there and not taking part in this reaction, this leads to a small inversion in the μ gradient. The inversion is tiny (Fig. 3): It is in about the fourth decimal place. Our three-dimensional (3D) modeling, however, shows the inversion to be hydrodynamically unstable, as we should expect from the classic Rayleigh-Taylor instability.

At a stage (Fig. 3) when the SCZ has just begun to retreat, there is no bump in 1/μ, but just a slight distortion at about 0.286 $M_\odot$. This is because the ^{3}He consumption is taking place in a region where there is still a substantial μ gradient left over from earlier history. As the H-burning shell moves out (in mass), though, the ^{3}He-burning shell preceding it moves into a region of more uniform ^{1}H/^{4}He ratio, so the peak in 1/μ begins to stand out. By the time the leading edge of the shell has moved to 0.29 $M_\odot$, there is a clear local maximum in 1/μ, which persists indefinitely as the H-burning shell advances and the convective envelope retreats.

At a point somewhat beyond this in the evolution of our 1D star (Fig. 1), we mapped the 1D model onto a 3D model and used the hydrodynamic code "Djehuty" developed at Lawrence Livermore National Laboratory (*10*–*12*). [The code is described most fully in (*12*).] Although Djehuty is designed to deal with an entire star,

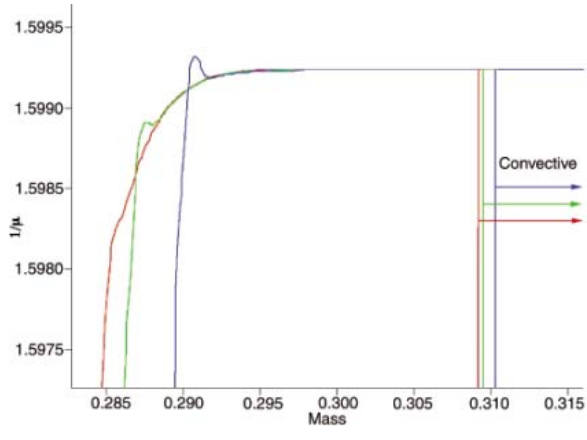

Fig. 3. The profile of reciprocal molecular weight (1/μ), as a function of mass in solar units, at three successive times (red, then green 2 million years later, then blue 2 million years later still).

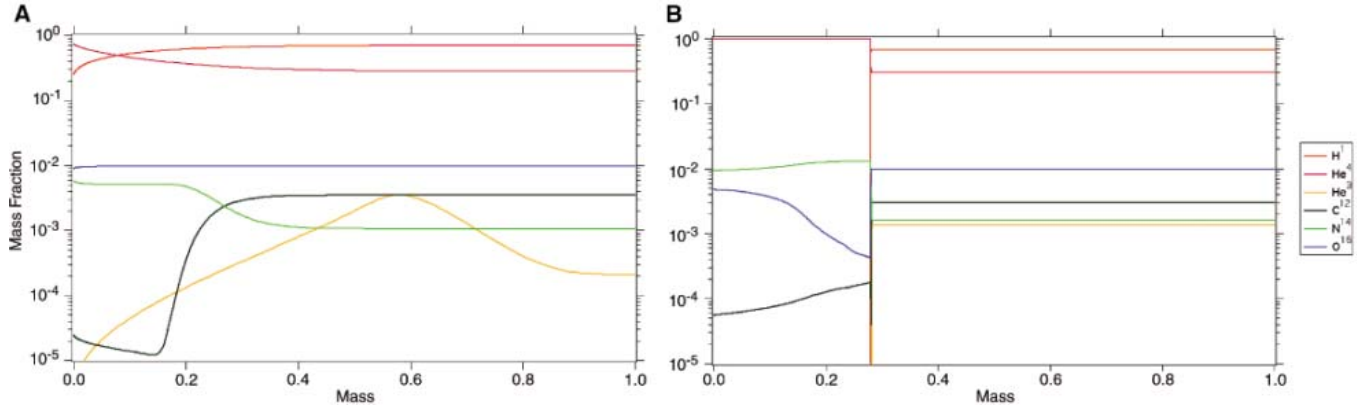

Fig. 2. (**A**) Profiles of the abundances of certain nuclei in a star that has evolved to roughly the end of the MS (Fig. 1) (T ~ 5000 K; L ~ 2 $L_\odot$). ^{1}H is orange, ^{4}He is red, ^{16}O is blue, ^{12}C is black, ^{14}N is green, and ^{3}He is yellow. ^{3}He shows a major peak where the abundance reaches ~18 times the initial (surface) abundance. (**B**) The same star later, when the SCZ reaches its maximum inward extent (Fig. 1). The ^{3}He peak has been homogenized to a factor of 8 larger than its initial value. The inert, H-depleted core is about 0.27 $M_\odot$.

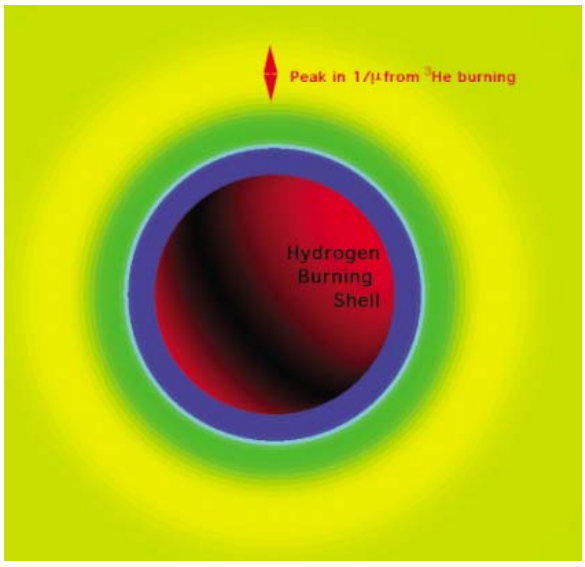

Fig. 4. A color-coded plot of μ on a cross-section through the initial 3D model. The shell where the μ inversion occurs is the yellow region sandwiched between a yellow-green and a darker green. The inversion is at a radius of ~5×10^7 m. The base of the SCZ is at ~2×10^9 m, well outside the frame, and the surface of the star is at ~2×10^{10} m.

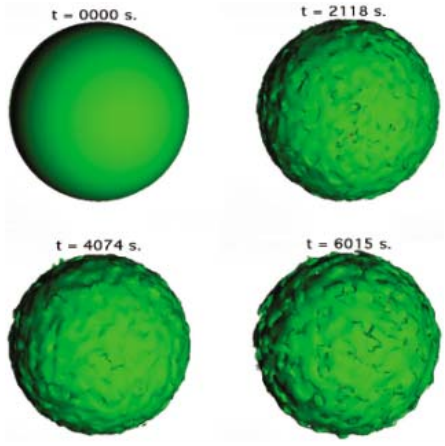

Fig. 5. The development with time of a contour surface of mean molecular weight near the peak in the blue curve of Fig. 3. The contour dimples, and begins to break up, on a time scale of only ~2000 s.

from center to photosphere, we economized on mesh points by considering only the region below the SCZ. It is important for numerical purposes that the 1D and 3D codes use exactly the same approximations for physical processes, for example, equation of state, nuclear reaction rates, and opacities.

The location of the starting model of the 3D calculation is shown in Fig. 1. If we had been clear before starting the 3D calculation that the 1/μ bump was going to cause mixing, we would have started further down, at the point where the bump first presents itself, which is just above the point labeled "deepest penetration of convection." It has become clear that our unexpected mixing will begin around here, and in practice we expect that almost all of the ^{3}He in the SCZ will have been consumed by the time the model reaches the point where our 3D calculation started. Because 3D modeling is very expensive of computer time, we have chosen not to redo the calculation for an earlier starting point. Figure 4 is a cross-section of the starting model for the 3D run and shows the μ inversion as a ring well outside the burning shell.

After the early development of the initially spherical shell on which 1/μ has a constant value near its peak (Fig. 5), the surface has begun to dimple after only ~800 s, and by 2118 s the dimpling is very marked and the surface has begun to tear. Some points have moved ~2% radially, that is, ~10^6 m, indicating velocities of ~500 m/s. The mean velocity decreases slightly in the passage from the second to the fourth panel. Other spherical shells, well away from the inversion on either side, show no such dimpling, at least until the influence of the inversion has spread to them. A movie of which Fig. 5 is four frames is given as Movie S1 in the Supporting Online Material.

The velocity we see is roughly consistent with the expectation that it should be $v^2 \sim g\, l\, \Delta\mu/\mu$, where g is the local gravity and l is the local pressure scale height. The motion appears turbulent and has the effect of diluting the inverse molecular-weight gradient, but it cannot eliminate it. As the turbulent region entrains more of the normally stable region outside it, yet below the normal convective envelope, it brings in fresh ^{3}He, which burns at the base of this mixing region, thus sustaining the inverse molecular-weight gradient. Ultimately this turbulent region will extend to unite with the normally convective envelope, so that the considerable reservoir of ^{3}He there will also be depleted. If its speed of ~500 m/s is maintained, the time for processed material to reach the classically unstable SCZ is only about 1 month, whereas the time for the H-burning shell to burn through the ~0.02 $M_\odot$ layer is more than 10^6 years.

The above argument establishes that the mixing in the SCZ is extended below the classical convective limit and that it is very fast compared with the nuclear time scales of either the hydrogen-burning shell or the ^{3}He-burning reaction. We estimate from the nuclear-burning rates that as the hydrogen shell burns outwards the ^{3}He will be destroyed in 16 times as much mass as the hydrogen shell burns through.

We believe that the extra mixing that we have seen gives a satisfactory answer to the problem of matching the ^{3}He abundance of Big Bang nucleosynthesis. Although low-mass stars do indeed produce considerable amounts of ^{3}He on the MS, this will all be destroyed by the substantially deeper mixing that we now expect on the RGB.

Our deeper mixing can also be relevant to further problems. According to the classical models of RGB stars, there is no further modification to the composition in an RGB convective envelope after it has reached its maximum extent early on the RGB. Yet observations persistently suggest that the ratios ^{13}C/^{12}C and ^{14}N/^{12}C both increase appreciably as one goes up the RGB (*13*, *14*). Both these ratios can be expected to increase only if the material in the envelope is somehow being processed near the H-burning shell. Our model makes this very likely. Although the μ inversion that we find is somewhat above the main part of the H-burning shell, it is not far above, and we can expect some modest processing of ^{12}C to ^{13}C and ^{14}N. According to (*15*), it appears to be necessary for some extra mixing to take place beyond the point on the RGB where the SCZ has penetrated most deeply; that is exactly the point where our mechanism should start to operate. In (*15*–*18*) it was suggested that rotation in the region between the SCZ and the hydrogen-burning shell might be responsible for the required mixing. We do not dispute the possible importance of rotation; however, we emphasize that the mechanism we have discovered is not ad hoc but simply arises naturally when the modeling is done in 3D. This mixing occurs regardless of possible variables like rotation and magnetic fields. It seems possible to us that different rates of rotation might vary the efficiency of our process, and we intend to investigate models with rotation in the future.

Correlations between abundance excesses and deficits of various elements and isotopes in the low-mass evolved stars of globular clusters have been reported in (*13*). Although it is hard to distinguish star-to-star variations that may be due to evolution from those that may be due to primordial variation, we expect our mechanism to lead to substantial evolutionary variations.

Our investigation demonstrates particularly clearly the virtue of attempting to model in 3D, where the motion evolved naturally and to a magnitude that was unexpected.

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above would be a factor of ~16 if we started with half as much ^{3}He, but the abundance level of ~1.6×10^{-3} would be very much the same.
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Supporting Online Material
www.sciencemag.org/cgi/content/full/1133065/DC1
Movie S1

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Operation of a DNA Robot Arm Inserted into a 2D DNA Crystalline Substrate

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The success of nanorobotics requires the precise placement and subsequent operation of specific nanomechanical devices at particular locations. The structural programmability of DNA makes it a particularly attractive system for nanorobotics. We have developed a cassette that enables the placement of a robust, sequence-dependent DNA robot arm within a two-dimensional (2D) crystalline DNA array. The cassette contains the device, an attachment site, and a reporter of state. We used atomic force microscopy to demonstrate that the rotary device is fully functional after insertion. Thus, a nanomechanical device can operate within a fixed frame of reference.

Branched DNA has proved to be a very useful and exciting medium for nanotechnology (*1*). This is a consequence of the programmability of DNA topology and three-dimensional (3D) structure through sequence, combined with the well-defined local structure of intermolecular association that occurs via sticky-ended cohesion (*2*). The development of stiff motifs (*3*) has enabled the self-assembly of DNA components to produce 2D arrays of high quality at atomic force microscopy (AFM) resolutions (*4*). In a separate but related thread, robust, sequence-dependent DNA nanomechanical devices have also been developed. The insertion of such nanomechanical devices into 2D arrays results in a nanorobotic system, wherein nanoscale moving parts can be controlled relative to a fixed frame of reference. We report the development of a cassette that contains both a rotary device and the features that enable its insertion into an array at a specific site. A change in the device control sequences or in the insertion sequences would result, respectively, in different controlling elements or in a different site of insertion, all within the context of the same cassette motif.

The PX-JX$_2$ device is a robust, sequence-dependent DNA machine whose state is controlled by hybridization topology (*5*). It can assume two structural states [termed PX (paranemic crossover) and JX$_2$ (paranemic crossover with two juxtaposed sites)] that differ from each other by a half-turn rotation of one end of the molecule relative to the other end. Two different pairs of set strands can bind to the framework

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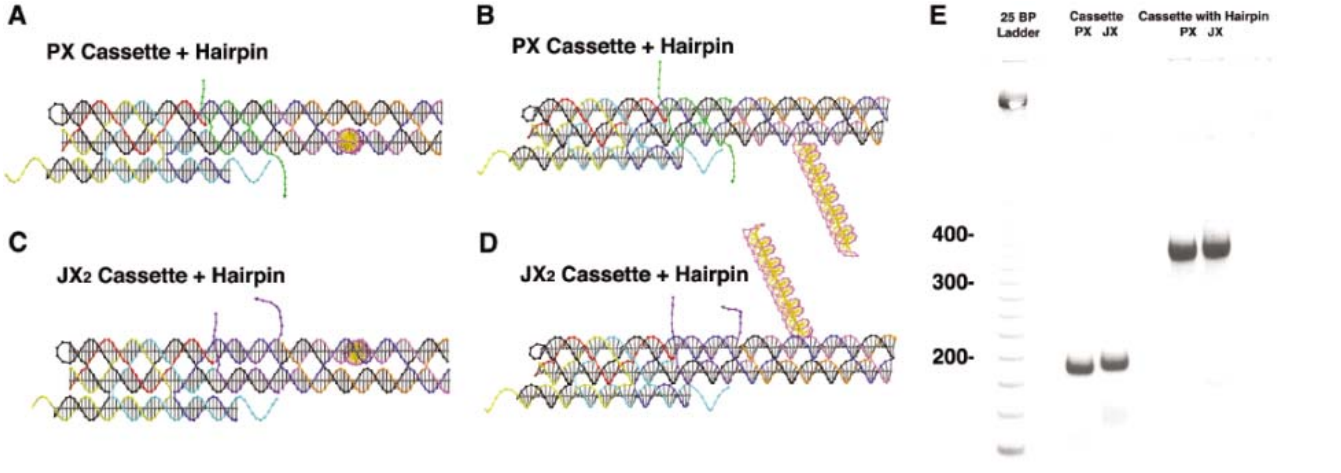

Fig. 1. (**A**) A view perpendicular to the plane of the cassette in the PX state. The PX state is set by the green strands in the middle of the upper two domains. The reporter hairpin is seen end-on protruding from the plane. The sticky ends on the bottom domain attach the cassette to the 2D array. (**B**) The same molecule is shown obliquely so the reporter hairpin can be seen. (**C**) A view similar to (A), except that the cassette is in the JX$_2$ state, which is set by the purple strands. The reporter hairpin is now behind the cassette, a point emphasized in (**D**). All drawings are in a virtual-bond representation produced by the program GIDEON (*13*). (**E**) A 5% polyacrylamide gel run in TAEM$_g$ buffer (*3*). The two different states are shown both for a cassette without a hairpin and for a cassette including a reporter hairpin. The single bands in each lane indicate that the motifs are stable and monodisperse. BP, base pair.

of the device, thereby establishing which structural state it adopts. Different devices can be addressed independently, leading to 2^N structural states if N devices are present (*6*). We showed by AFM that the PX-JX_2 device is functional after the cassette has been inserted into a 2D DNA array. The cassette used here also contains a component that reports its state, although that is not a general requirement.

The cassette that we have developed is shown schematically in both of its states in Fig. 1. A and B show the cassette plus a reporter hairpin in the PX state: A is perpendicular to its plane, and B is oblique; C and D show similar views of the JX_2 state. The cassette consists of three helical domains, one of which is much shorter than the other two. The short domain, shown on the bottom in Fig. 1, A to D, is the insertion domain. It contains sticky ends that enable its cohesion roughly perpendicular (three nucleotide pairs rotation, ~103°) to the array that supports it. This

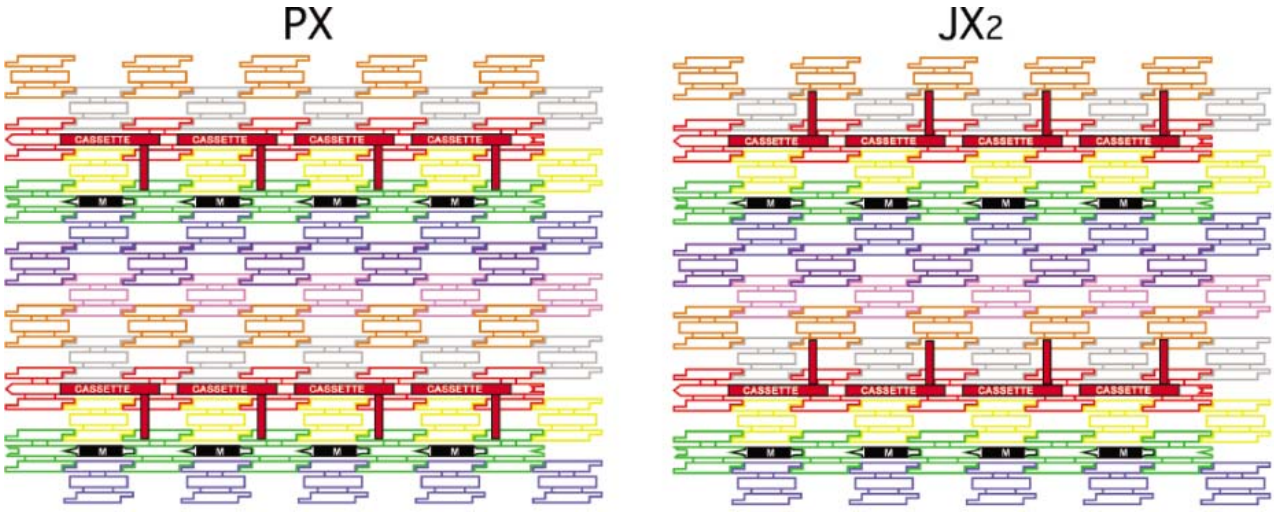

Fig. 2. The arrays are shown schematically to demonstrate the two states of the device in the cassette. The eight TX tiles that form the array are shown in differently colored outlined tiles. For clarity, the cohesive ends are shown to be the same geometrical shape, although they all contain different sequences. The cassette and reporter helix are shown as solid red components; the marker tile is labeled M and is shown with a solid black rectangle representing the domain of the tile that protrudes from the rest of the array. Both the cassette and the marker tile are rotated ~103° from the other components of the array (three nucleotides rotation). The PX arrangement is shown on the left, and the JX_2 arrangement is on the right. The reporter hairpin points toward the marker tile in the PX state but points away from it in the JX_2 state.

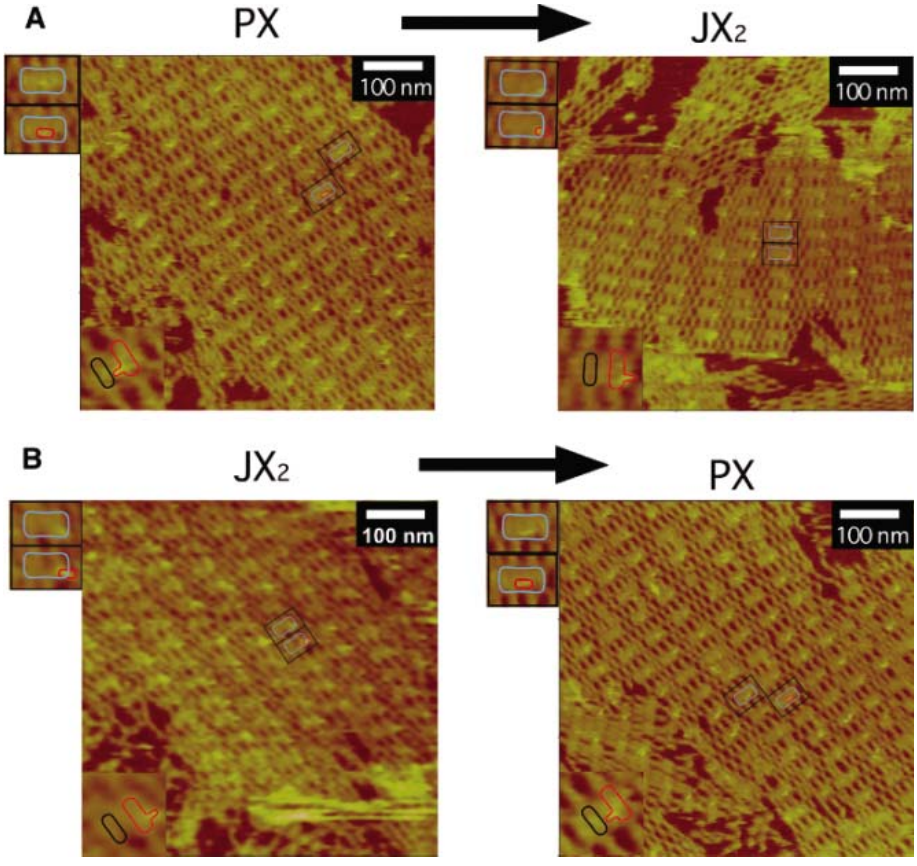

Fig. 3. (**A**) Conversion of the array in the PX state to the array in the JX_2 state. (**B**) The reverse motion, JX_2 to PX. The scales of the AFM images are indicated by a 100-nm scale bar in the upper right of each image. In both states, the cassette and the marker tile are visible as a doubly lobed blob-like region. In the PX state, the reporter hairpin is visible as a bright spot at the center of the blob. In the JX_2 state, the reporter arm is visible as a bright spot on one edge of the blob. We have emphasized these features on the four images: In each image, we have drawn a black box around the unit cell repeat in two cases and a blue rounded figure encircling the blob-like region. In one of the two boxes, we have emphasized the reporter arm by enclosing it in a red circle. Expanded, upright double-scale copies of these boxes are shown adjoining the upper left edge of each image. In addition, in the lower left corner of each image, we have taken a 50 by 50-nm portion of the image, circled the marker in a black ellipse, and enclosed the cassette with a red curve that has a protrusion corresponding to the reporter hairpin. The right side of each pair of images is from an aliquot taken from a solution of the material on the left and then converted to the other state.

domain is connected to the middle domain by a DAO (double crossover with antiparallel helices whose crossovers are separated by an odd number of DNA half-turns) linkage (*3*). In contrast, the central domain is connected to the upper domain by a PX linkage (*7*). Further right on the upper domains, the double-helical continuity is interrupted by a pair of set strands (green in A and B, purple in C and D) that controls the state of the PX-JX_2 device. Proceeding to the right, the two-helix motif continues for about four double-helical turns. A long reporter hairpin has been attached so that it extends perpendicular to the plane of the cassette. This hairpin points in opposite directions in the PX state and in the JX_2 state, enabling differentiation of the two states by means of AFM. The stability of the cassette in both states, with and without the reporter hairpin, is indicated by the presence of single bands on a nondenaturing gel in Fig. 1E.

A three-domain tile (TX) array (*8*) was selected for insertion. In this array, the TX tiles are connected so that the bottom domain of each tile is attached to the upper domain of a tile in an adjacent column (Fig. 2). This arrangement produces slots that may be flanked by sticky ends on the termini of the middle domains of each TX tile. These sticky ends can be used to bind another tile with complementary sticky ends in that site (*8*). We form the TX array with eight unique tiles, so as to accommodate the cassette's long reporter hairpin (Fig. 1); the size of the hairpin needed to demonstrate motion has limited us to only two inserted elements. One of these elements is the cassette, containing the PX-JX_2 device, and the other is a TX marker tile, parallel to the cassette, that enables us to establish a reference frame on the array. The marker tile is in the same column as the cassette insertion domain (Fig. 2). The sequences of the cassette and the tiles are shown in fig. S1; the presence of all strands in each state is shown in figs. S2 and S3; the conversion of state in solution is shown in fig. S4 (*9*).

The results of insertion and state conversion are shown by AFM in Fig. 3. Fig. 3A shows an array of PX-state cassettes (left) that have been converted to JX_2-state cassettes (right); Fig. 3B shows the reverse conversion, where an array formed with JX_2-state cassettes (left) is converted to cassettes in the PX state (right). It is important to recognize that these conversions occur after the cassettes have been inserted into the array [detailed methods are described in (*9*)]. In addition to the arrays shown in Fig. 3, we have examined two other sets of inserted cassette arrays (figs. S5 and S6) (*9*). As summarized in table S1 (*9*), the AFM images are only good enough to ascertain the states of about half of the pretransition cassettes and slightly fewer of the posttransition cassettes. Among the three image sets (Figs. 3 and figs. S5 and S6), we detected no errors in the pretransition arrays. After conversion from the PX state, 95 of 96 cassettes are seen correctly in the JX_2 state; after conversion from the JX_2 state, 85 of 86 cassettes are seen correctly in the PX state, suggesting a conversion error rate ~1%.

It is crucial for nanorobotics to be able to insert controllable devices into a substrate, thereby leading to a diversity of structural states. Here we have demonstrated that a single device has been inserted and converted at a specific site. There is no reason to expect that the system is limited to a single device unit; as noted above, the specific addressability of the two-state PX-JX_2 device has been demonstrated previously (*6*). It has been pointed out that two opposing PX-JX_2 devices could be used to produce complex patterns (*10*). The eight-tile TX array used here is technically difficult to obtain, but the recent advance in simplified 2D DNA patterning by Rothemund (*11*) should facilitate the construction of complex base planes for these systems. Similarly, DNA tubes (*12*) provide a means to incorporate nanomechanical devices into nonplanar 2D arrangements.

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Supporting Online Material

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Materials and Methods
SOM Text
Figs. S1 to S6
Table S1
References

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Enzyme-Free Nucleic Acid Logic Circuits

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Biological organisms perform complex information processing and control tasks using sophisticated biochemical circuits, yet the engineering of such circuits remains ineffective compared with that of electronic circuits. To systematically create complex yet reliable circuits, electrical engineers use digital logic, wherein gates and subcircuits are composed modularly and signal restoration prevents signal degradation. We report the design and experimental implementation of DNA-based digital logic circuits. We demonstrate AND, OR, and NOT gates, signal restoration, amplification, feedback, and cascading. Gate design and circuit construction is modular. The gates use single-stranded nucleic acids as inputs and outputs, and the mechanism relies exclusively on sequence recognition and strand displacement. Biological nucleic acids such as microRNAs can serve as inputs, suggesting applications in biotechnology and bioengineering.

To date, no man-made chemical circuits even remotely approach the complexity and reliability of silicon-based electronics. Once reliable principles for their design are established, synthetic chemical circuits could be used routinely to control nanoscale devices in vitro, to analyze complex chemical samples in situ, or to interface with existing biological circuits in vivo (*1*). Construction of synthetic biological circuits de novo is a powerful test of design principles (*2*).

Rational design of nucleic acid devices is simplified by the predictability of Watson-Crick base pairing; thus, nucleic acids are a promising alternative to proteins for synthetic chemical circuits. Allosteric ribozymes that take small molecules as input have been shown to perform logical functions (*3*). However, their output (a cleaved or ligated oligonucleotide) is of a different form than the input; hence, cascading is difficult. Automata performing multiple logical operations in parallel (*4*), single-step signaling cascades (*5*),

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and a feedback cycle that acts as an exponential chain reaction (*6*) were built using deoxyribozymes controlled by input oligonucleotides (*7*). Another approach uses sequence recognition to control enzyme catalysis of covalent bond formation and breakage (*8*–*10*). Alternatively, nucleic acid reactions can be driven without enzyme or (deoxy)ribozyme catalysis (*11*, *12*); this principle has been exploited to construct DNA-based logic gates and signaling cascades (*13*, *14*). Such molecular automata may give rise to "smart" therapeutics for medical applications (*7*, *9*, *10*). Recently, engineered nucleic acid logic switches based on hybridization and conformational changes have been successfully demonstrated in vivo (*15*, *16*). The remaining challenge is to design chemical logic gates that can be combined to construct large, reliable circuits. The analogous challenge for engineering electronic circuits was met by the development of digital design principles (*17*); these may also prove essential for designing complex yet robust chemical circuits.

We report the construction of in vitro DNA-based logic gates and circuits that embody digital design principles: logic, cascading, restoration, fan-out, and modularity. These circuits implement a complete set of Boolean logic functions (AND, OR, and NOT) using short oligonucleotides as input and output. Because the input and output are of the same form, the gates can be cascaded to create multilayer circuits. Logical values "0" and "1" are represented by low and high concentrations, respectively. Signal restoration is performed by threshold and amplifier gates that protect against noise, signal loss, and leaky reactions. Amplifier gates can also be used to ensure that a logic gate generates sufficient signal to drive multiple downstream targets. Watson-Crick interactions between modular recognition domains determine the connectivity of gates. Sequences can be chosen with few constraints, allowing the construction of arbitrary circuits with negligible cross-activation. Furthermore, modular construction allows for interfacing with existing molecular components—be they predesigned subcircuits or naturally occurring nucleic acids.

Gate function is entirely determined by base pairing and breaking. Every gate consists of one or more gate strands and one output strand (Fig. 1A and fig. S1). The output strand either serves as an input to a downstream gate or is modified with a dye label to provide a readout in a fluorescence experiment. Both ends of the output strand (Fig. 1A), or only one end (translator gates in Fig. 2), can be attached to the gate complex. Figure 1A shows an AND-gate assembled from an output strand and two gate strands. The addition of single-stranded inputs to a solution containing the gate initiates a computation. Each gate strand contains a recognition region that is complementary to its input. Initially, the recognition regions of all gate strands are double-stranded and therefore inert, except for the toehold farthest from the output strand (strand G in Fig. 1A). When the first input binds this toehold, it displaces the first gate strand by three-way branch migration (*18*, *19*), exposing the toehold for the subsequent input and releasing an inert double-stranded waste product. A similar process can now occur for the second input. The output strand is released if and only if both inputs are present. To implement this design, DNA sequences (tables S1 to S3) were selected to ensure correct complementarity while minimizing spurious interactions (*20*).

The two-input AND gate has four entries in its truth table (Fig. 1B) and was shown to function correctly when tested by fluorescence kinetics experiments and gel electrophoresis (Fig. 1, C and D). We also designed multi-input AND gates using the same principles and showed that they work reliably (fig. S2). The gates in all of our experiments were purified by gel electrophoresis after triggering "leaky" complexes (*20*) (fig. S3).

The output strand of one gate may be an input strand to a downstream gate. It is essential that the output strand not interact with downstream gates before release. Protecting the toehold binding region of output strands in upstream gates prevents such interactions. We built a circuit composed of one AND gate and two translator gates that demonstrates this principle (Fig. 2A and fig. S4). A translator gate converts the signal encoded in the input strand to the signal encoded in the output strand and is implemented as a single-input AND gate. The translator gates JK and LM translate two biological microRNA sequences (mouse let-7c and miR-124a) into outputs with recognition regions identical to strands G_{in} and F_{in}. The input to a translator gate and the recognition region of its output strand need only share sequence in the toehold region. If two translators are cascaded, then there is no sequence restriction between the initial input strand and the final output strand. This is called a full translator; the cascading of NO and HI is an example (Fig. 3 and fig. S1). Translators can connect subcircuits that do not a priori use the same sequences for the

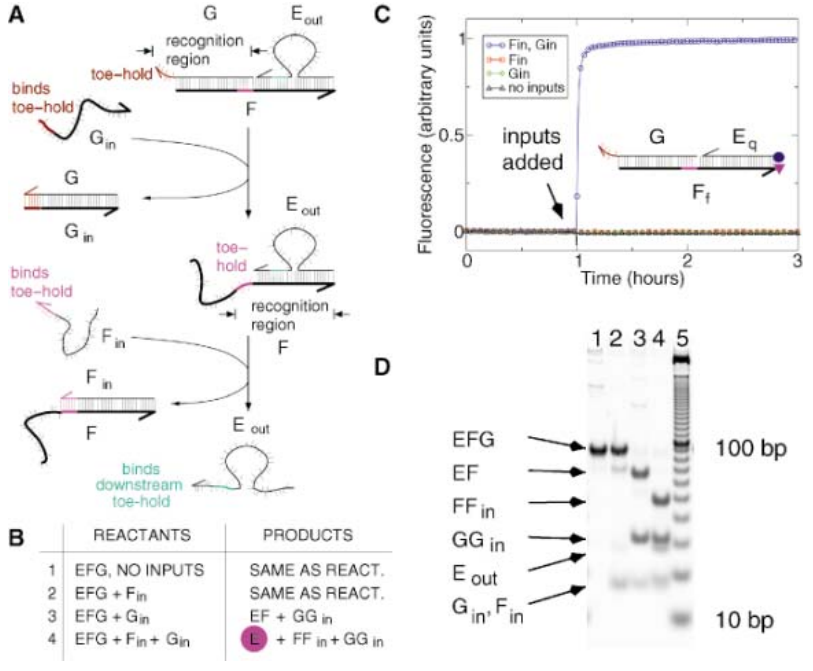

Fig. 1. Two-input AND gate. (**A**) The gate consists of three DNA strands, E_{out} [57 nucleotides (nt)], F (60 nt), and G (36 nt). The 3′ ends are marked by arrows. Toeholds and toehold binding regions (all six nucleotides) are indicated in color. Input strands F_{in} and G_{in} (36 nt) are complementary to recognition regions within the corresponding gate strands F and G. (**B**) Truth table for the two-input AND gate. The released output strand is highlighted. (**C**) In fluorescence experiments, strands F_f [carboxytetramethylrhodamine (TAMRA) fluorophore at the 3′ end] and E_q (Iowa Black RQ quencher at the 5′ end, without bulge loop) were used instead of F and E_{out} (see inset). Release of output strand results in increased fluorescence. Experiments were conducted at 25°C with gate concentrations of 250 nM and input concentrations of 300 nM in a Tris-acetate-EDTA buffer containing 12.5 mM Mg^{++}. (**D**) Nondenaturing gel electrophoresis directly confirms reaction intermediates and waste products for each possible input combination. Lanes 1 to 4: The samples are as described in entries 1 to 4 of the truth table. The gate used in this experiment is as shown in (A). Lane 5: 10–base pair (bp) ladder.

toehold and recognition regions. This is particularly useful for adapting an existing circuit to compute on arbitrary biological inputs.

The circuit of Fig. 2A was also tested under conditions relevant to potential biological applications. The circuit works comparably with RNA inputs as with DNA inputs because gate function depends solely on Watson-Crick complementarity (Fig. 2A and fig. S4). Increasing the temperature to 37°C does not degrade circuit performance. Finally, the circuit functions well in the presence of potentially interfering biological RNA (mouse brain total RNA) at a concentration in excess of gate complexes and input strands.

Because a small set of logic gates (AND, OR, and NOT) is sufficient for effective computation of any Boolean function, we developed DNA gates to perform these operations. Logical OR functionality is obtained by using two gates that produce the same output. We constructed a three-gate chemical circuit in which a logical OR feeds into a logical AND (fig. S4B). Acting as a logical OR, translator gates ST and UV take different inputs (miR-15a and miR-10b) but release outputs with identical recognition regions. If Boolean values are represented by the presence of either one strand ("0") or another strand ("1")—the so-called "dual-rail" representation (*21*)—then AND and OR are themselves sufficient to compute any Boolean function.

If a Boolean value is represented by the presence or absence of a single input strand, a NOT gate may be necessary. We modified the circuit shown in Fig. 2A to invert the let-7c input (Fig. 2B). The NOT gate makes use of an additional "inverter" strand that triggers the gate unless the input strand is present to act as a competitive inhibitor. Because the inverter strand must be added simultaneously with the input, NOT gates are restricted to the first layer of the circuit. This is sufficient to create a dual-rail representation from which arbitrary subsequent computation can be performed with just AND and OR.

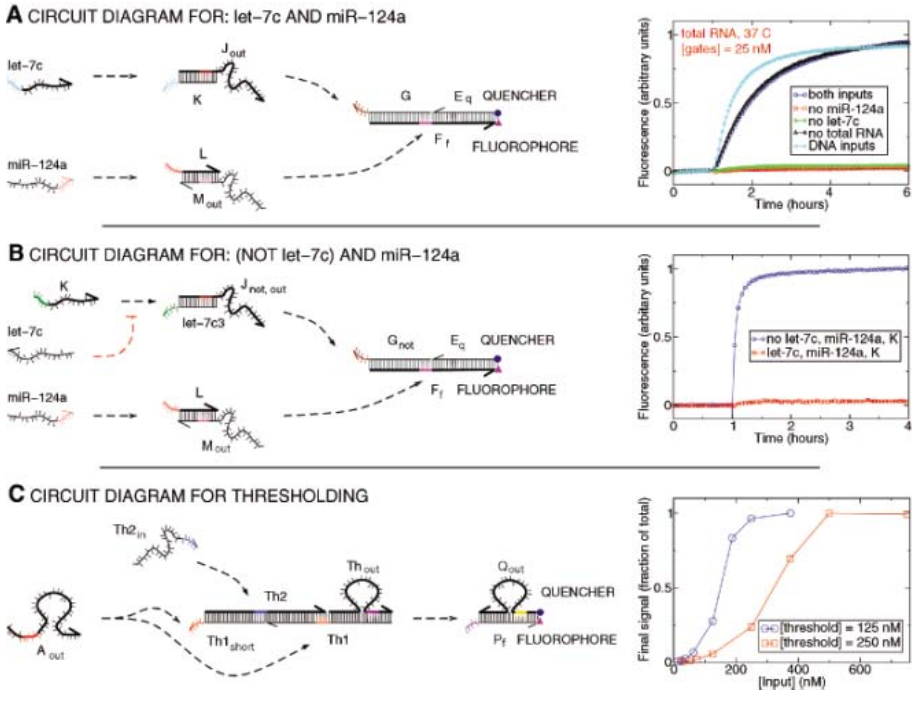

Fig. 2. Translator gates, NOT operation, and signal restoration. Dashed arrows indicate where input or output strands can serve as inputs to downstream gates. (**A**) Circuit operation at 37°C with RNA inputs and DNA gates in a total RNA background. All gates are at 25 nM, synthetic RNA inputs are at 30 nM, and total RNA (mouse brain) is at a concentration of 200 μg/ml. Proper function is observed. For comparison, experiments with no total RNA were performed, using either both RNA inputs or both DNA inputs. (**B**) The NOT gate consists of a translator gate and an inverter strand complementary to let-7c. Gate, inverter strand, and input concentrations are 250 nM, 300 nM, and 300 nM, respectively. Here and in all subsequent experiments, the temperature was 25°C and DNA equivalents of the biological microRNAs were used. If let-7c was present, inverter strand K preferentially hybridized to let-7c. Otherwise, inverter strand K triggered the translator. (**C**) The thresholding gate, using a dye/quencher-labeled readout gate to monitor the output. Strand $Th2_{in}$ is part of the thresholding unit and was added before the start of the experiment. The final fluorescence is plotted against the input concentration for two different concentrations of the threshold gate.

A gate may fail in two ways: It may fail to produce enough output when triggered, or it may "leak" by spontaneously releasing the output strand. Both types of error require signal restoration; the former requires increasing a moderate output amount to the full activation level, and the latter requires decreasing a small output amount to a negligible level. To implement signal restoration, we developed gates for amplification and thresholding. The threshold gate (Fig. 2C) is a three-input AND gate with identical first and third inputs. The second input is only necessary for structural purposes; it is always present and can be considered part of the thresholding unit. A substoichiometric amount of input (with respect to threshold gates) will cause most gates to lose only their first and second gate strands, thus releasing no output. Input concentrations two times as high as the concentration of threshold gates will cause most gates to produce output. The threshold gate's concentration sets the threshold for a sigmoidal nonlinearity (Fig. 2C and fig. S5) (*20*).

Because the threshold gate's output cannot exceed half the input signal, subsequent amplification is necessary. A hybridization-based system for catalytic amplification was demonstrated previously (*22*). With minor modifications, the system serves as both an input amplifier and full translator (fig. S6 and Fig. 3, left, miR-143 translator), or as a fluorescence readout (fig. S7A and Fig. 3, right). Alternatively, amplifiers based on feedback logic can be designed (fig. S6B). A threshold gate together with an amplifier gate constitutes a signal restoration module whose incorporation into large circuits at multiple intermediate points ensures the stability of digital representation (*23*).

Finally, to demonstrate modularity and scalability, we composed eleven gates into a larger circuit. The circuit combines previously introduced modules for input translation and amplification, calculation of AND and OR, and signal restoration (Fig. 3). The inputs to the circuit are DNA analogs of six mouse microRNAs. To determine the effectiveness of signal restoration, we constructed an equivalent circuit without signal restoration and tested both circuits with an input at one-quarter the strength of a signal that is fully on (0.25×) to simulate a large upstream leak. The complete circuit maintained a low output signal, whereas the circuit without signal restoration exhibited a ≈25% output leak (Fig. 3, inset). To verify other circuit components, several subcircuits were constructed and tested independently (figs. S8 and S9). The feedback fluorescence amplifier was tested as a replacement for the catalytic amplifier at the output, resulting in a circuit containing 12 gates (fig. S10).

As increasingly larger circuits are constructed, speed becomes a limiting factor. The circuit without signal restoration takes 2 hours

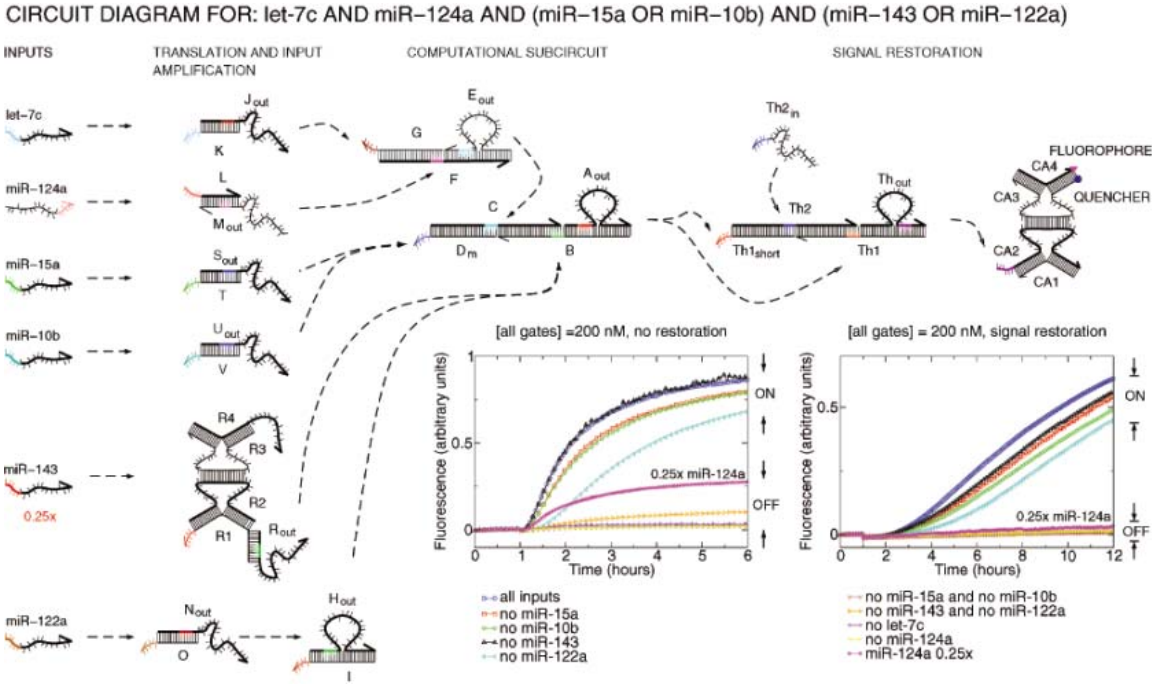

Fig. 3. Signal propagation through a complex chemical circuit combining AND, OR, sequence translation, input amplification, and signal restoration. The five-layer circuit consists of a total of 11 gates and accepts six inputs. With the exception of the threshold gate, which was at 100 nM with its $Th2_{in}$ strand at 150 nM, all gates were at 200 nM (1×) per gate. Unless otherwise specified, inputs were added at 250 nM (1.25×). miR-143 was added at 50 nM (0.25×) and subsequently amplified by the input amplifier. (Inset) Fluorescence traces of circuit operation without and with the signal restoration module (threshold plus amplifier). The traces for input conditions corresponding to a logical TRUE output (ON) are clearly distinguishable from the logical FALSE output (OFF). Cases tested include when all inputs are present, all cases in which exactly one input is missing, and combinations of inputs that turn off an OR clause. Assuming monotonicity, withholding additional inputs will never lead to a logical TRUE output. To determine the response of the circuit to a leaky OFF signal, input miR-124a was added at 50 nM (0.25×) while all other inputs were added normally.

to reach half-activation (Fig. 3, left inset). The circuit with signal restoration has two additional layers and takes 10 hours to achieve half-activation (Fig. 3, right inset). Despite the slow operation, in both cases a clear difference between off and on states can be distinguished much earlier. Speeding up the responses of individual gates (e.g., by shortening recognition domains) or changing other reaction conditions may improve overall circuit performance.

Our success in creating large circuits can be attributed to adherence to the tenets of digital logic, toehold sequestering combined with branch migration and strand displacement, reduction of leak reactions by purification, and modularity of design. The logic gates developed here and the principles on which they are based can also be used to construct analog or hybrid circuits (*24*) and are likely to prove compatible with other approaches to building molecular automata in vitro and in vivo (*5*, *7*–*9*, *13*, *15*, *16*). Because evidence suggests that our logic gates can use natural RNA as input and that they behave correctly in the presence of mouse total RNA, our hybridization-based circuits might be adapted for in situ detection of complex expression patterns or even in vivo logic processing.

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17. In contrast to digital electronic circuits, analog electronic circuits have not advanced rapidly because circuit design remains more "art" than systematic engineering, making the construction of large reliable circuits difficult. This is often attributed to the lack of the digital abstraction: In analog circuits even slight signal changes carry meaning (e.g., the value is 5.2 not 5.3) and thus restoration to clean up noise or gate malfunction is not possible. The lack of restoration also complicates circuit modularity, because circuit behavior can be subtly changed when subcircuits are combined (*24*).
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Materials and Methods
Figs. S1 to S10
Tables S1 to S3

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Microwave-Induced Cooling of a Superconducting Qubit

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We demonstrated microwave-induced cooling in a superconducting flux qubit. The thermal population in the first-excited state of the qubit is driven to a higher-excited state by way of a sideband transition. Subsequent relaxation into the ground state results in cooling. Effective temperatures as low as ≈3 millikelvin are achieved for bath temperatures of 30 to 400 millikelvin, a cooling factor between 10 and 100. This demonstration provides an analog to optical cooling of trapped ions and atoms and is generalizable to other solid-state quantum systems. Active cooling of qubits, applied to quantum information science, provides a means for qubit-state preparation with improved fidelity and for suppressing decoherence in multi-qubit systems.

Cooling dramatically affects the quantum dynamics of a system, suppressing dephasing and noise processes and revealing an array of lower-energy quantum-coherent phenomena, such as superfluidity, superconductivity, and the Josephson effect. Conventionally, the entire system under study is cooled with ^{3}He-^{4}He cryogenic techniques. Although this straightforward approach has advantages, such as cooling ancillary electronics and providing thermal stability, it also has drawbacks. In particular, limited cooling efficiency and poor heat conduction at millikelvin temperatures limit the lowest temperatures attainable.

A fundamentally different approach to cooling has been developed and implemented in quantum optics (*1*–*4*). The key idea is that the degrees of freedom of interest may be cooled individually, without relying on heat transfer among different parts of the system. By such directed cooling processes, the temperature of individual quantum states can be reduced by many orders of magnitude with little effect on the temperature of surrounding degrees of freedom. In one successful approach, called sideband cooling (*5*–*8*), the unwanted thermal population of an excited state $|1\rangle$ is eliminated by driving a resonant sideband transition to a higher excited state $|2\rangle$, whose population quickly relaxes into the ground state $|0\rangle$ (Fig. 1A). The two-level subsystem of interest, here $\{|0\rangle, |1\rangle\}$, is efficiently cooled if the driving-induced population transfer to state $|0\rangle$ is faster than the thermal repopulation of state $|1\rangle$. The sideband method, originally used to cool vibrational states of trapped ions and atoms, allows several interesting extensions (*1*–*4*, *9*–*12*). For example, the transition to an excited state can be achieved by nonresonant processes, such as adiabatic passage (*9*), or by adiabatic evolution in an optical potential (*10*–*12*). Other approaches, such as optical molasses and evaporative cooling, have been developed to cool the translational degrees of freedom of atoms to nanokelvin temperatures, establishing the basis for the modern physics of cold atoms (*13*).

Superconducting qubits are mesoscopic artificial atoms (*14*) that exhibit quantum-coherent dynamics (*15*) and host a number of phenomena known to atomic physics and quantum optics, including coherent quantum superpositions of distinct macroscopic states (*16*, *17*), time-dependent Rabi oscillations (*18*–*24*), coherent coupling to microwave cavity photons (*25*–*27*), and Stückelberg oscillations via Mach-Zehnder interferometry (*28*–*30*). In a number of these experiments, qubit state preparation by a dc pulse or by thermalization with the bath was used. It is tempting, however, to extend the ideas and benefits of optical cooling to solid-state qubits, because they present a high degree of quantum coherence, a relatively strong coupling to external fields, and tunability, a combination rarely found in other fundamental quantum systems.

We demonstrate a solid-state analog to optical cooling by using a niobium persistent-current qubit (*31*), a superconducting loop interrupted by three Josephson junctions (*32*). When the qubit loop is threaded with a dc magnetic flux $f_q \approx \Phi_0/2$, where $\Phi_0 \equiv h/2e$ is the flux quantum (h is Planck's constant), the qubit's potential energy exhibits a double-well profile (Fig. 1A), which can be tilted by adjusting the flux detuning, $\delta f_q = f_q - \Phi_0/2$, away from zero. The lowest-energy states of each

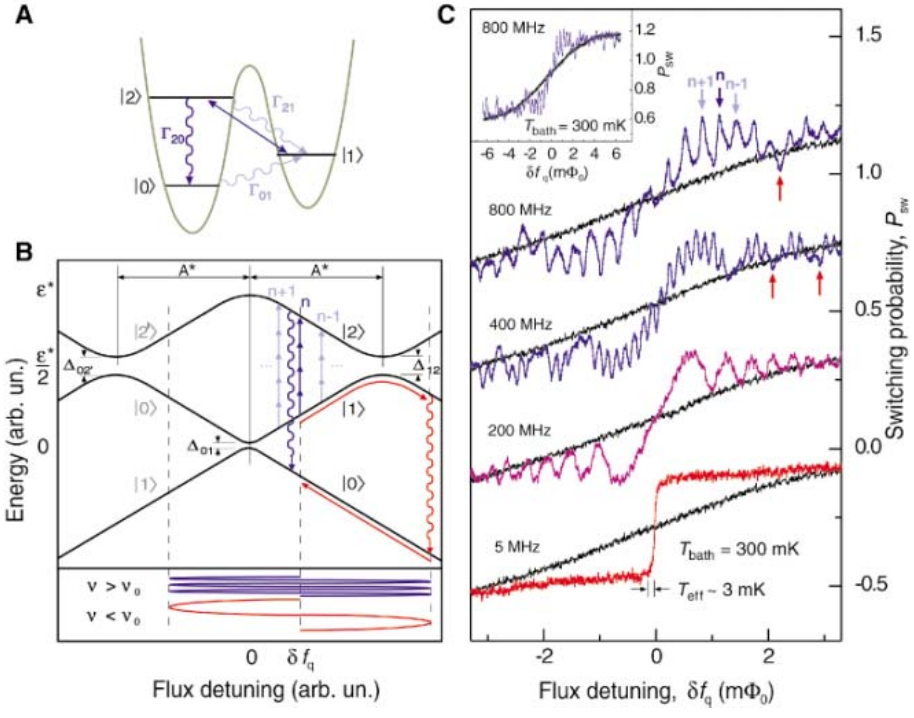

Fig. 1. Sideband cooling in a flux qubit. (**A**) External excitation transfers the thermal population from state $|1\rangle$ to state $|2\rangle$ (straight line) from which it decays into the ground state $|0\rangle$. Wavy lines represent spontaneous relaxation and absorption, $\Gamma_{20} >> \Gamma_{21},\Gamma_{01}$. The double well is the flux-qubit potential comprising energy levels. (**B**) Schematic band diagram illustrating the resonant and adiabatic sideband cooling of the ac-driven qubit. $|1\rangle \rightarrow |2\rangle$ transitions are resonant at high driving frequency ν (blue lines) and occur via adiabatic passage at low ν (red lines). Δ_{01} and Δ_{12} are the tunnel splittings between $|0\rangle$ and $|1\rangle$ and between $|1\rangle$ and $|2\rangle$. (**C**) Cooling induced by ac-pulses with driving frequencies ν = 800, 400, 200, and 5 MHz. State $|0\rangle$ population P_{sw} versus flux detuning δf_q for the cooled qubit and for the qubit in thermal equilibrium with the bath (black lines, T_{bath} = 300 mK). Measurements for ν = 800, 200, and 5 MHz are displaced vertically for clarity. (Inset) P_{sw} versus δf_q over a wider range of flux detuning; ν = 800 MHz.

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well are the diabatic qubit states of interest, $|0\rangle$ and $|1\rangle$, characterized by persistent currents I_q with opposing circulation, whereas the higher-excited states in each well, e.g., $|2\rangle$, are ancillary levels that form the "sideband transition" with the qubit. In contrast to conventional sideband cooling, which aims to cool an "external" harmonic oscillator (e.g., ion trap potential) with an "internal" qubit (e.g., two-level system in an ion), our demonstration aims to cool an "internal" qubit by using an ancillary "internal" oscillator-like state [supporting online material (SOM) Text].

When the qubit is in equilibrium with its environment, some population is thermally excited from the ground-state $|0\rangle$ to state $|1\rangle$ according to $p_1/p_0 = \exp[-(\varepsilon_1 - \varepsilon_0)/k_B T_{bath}]$, where $p_{0,1}$ are the qubit populations for energy levels $\varepsilon_{0,1}$, k_B is the Boltzmann constant, and T_{bath} is the bath temperature. To cool the qubit subsystem below T_{bath}, in analogy to optical pumping and sideband cooling, a microwave magnetic flux of amplitude A and frequency ν targets the $|1\rangle \longrightarrow |2\rangle$ transition, driving the state $|1\rangle$ thermal population to state $|2\rangle$, from which it quickly relaxes to the ground state $|0\rangle$. The hierarchy of relaxation and absorption rates required for efficient cooling, $\Gamma_{20} >> \Gamma_{21},\Gamma_{01}$, is achieved in our system owing to a relatively weak tunneling between wells, which inhibits the interwell relaxation and absorption processes, $|2\rangle \longrightarrow |1\rangle$ and $|0\rangle \longrightarrow |1\rangle$, compared with the relatively strong intrawell relaxation process, $|2\rangle \longrightarrow |0\rangle$. This three-level system behavior is markedly different from the population saturation observed in two-level systems.

The cooling procedure illustrated in Fig. 1A is generalized to the energy-band diagram shown schematically in Fig. 1B. The diabatic-state energies

$$\varepsilon_{1,0} = \pm I_q \delta f_q, \quad \varepsilon_{2',2} = \varepsilon^* \pm I_q \delta f_q \qquad (1)$$

are linear in the flux detuning δf_q, with the energy $\varepsilon^* \approx 25$ GHz and $I_q = 1.44$ GHz/mΦ_0 in our device, and exhibit avoided crossings $\Delta_{01} \approx 12$ MHz and $\Delta_{12} = \Delta_{02'} \approx 100$ MHz due to quantum tunneling through the double-well barrier (Fig. 1A). The diabatic levels exchange roles at each avoided crossing, and the energy band is symmetric about $\delta f_q = 0$ (*33*).

Under equilibrium conditions, the average level populations exhibit a thermally broadened "qubit step" about $\delta f_q = 0$, the location of the $|0\rangle$ to $|1\rangle$ avoided crossing. This is determined from the switching probability P_{sw} of the measurement superconducting quantum interference device (SQUID) magnetometer, which follows the $|0\rangle$ state population (*32*)

$$P_{sw} = \frac{1}{2}(1 + F m_0), \quad m_0 = \tanh\frac{\varepsilon}{2k_B T} \qquad (2)$$

where F is the fidelity of the measurement, $m_0 = p_0 - p_1$ is the equilibrium magnetization that results from the qubit populations $p_{0,1}$, $T = T_{bath}$, and $\varepsilon = \varepsilon_1 - \varepsilon_0 \propto \delta f_q$ as inferred from Eq. 1. In the presence of microwave excitation targeting the $|1\rangle \longrightarrow |2\rangle$ transition, the resultant cooling, which we will later quantify in terms of an effective temperature $T_{eff} < T_{bath}$, acts to increase the ground-state population and, thereby, sharpen the qubit step. This cooling signature is evident in Fig. 1C, where we show the qubit step before and after applying a cooling pulse at several frequencies for $T_{bath} = 300$ mK.

The cooling presented in Fig. 1, B and C, exhibits a rich structure as a function of driving frequency and detuning, resulting from the manner in which state $|2\rangle$ is accessed. The $|1\rangle \longrightarrow |2\rangle$ transition rate can be described by a product of a resonant factor and an oscillatory Airy factor (*30*). The former dominates at high frequencies (800 and 400 MHz), where well-resolved resonances of n-photon transitions are observed, as illustrated in Fig. 1B (transition in blue) and Fig. 1C (top traces and inset). The cooling is thus maximized near the detuning values matching $\varepsilon_2 - \varepsilon_1 = nh\nu$ (downward arrows in Fig. 1C). At intermediate frequencies (400 and 200 MHz), the Airy factor becomes more prominent and accounts for the Stückelberg-like oscillations that modulate the intensity of the n-photon resonances (*28*, *30*). Below $\nu = 200$ MHz, although individual resonances are no longer discernible, the modulation envelope persists due to the coherence of the Landau-Zener dynamics at the Δ_{12} avoided crossing (*30*). The $|1\rangle \longrightarrow |2\rangle$ transition becomes weak near the zeros of the modulation envelope, where we observe less efficient cooling, or even slight heating (e.g., upward arrows in Fig. 1C, 800 and 400 MHz). This is a result of the $|0\rangle \longrightarrow |1\rangle$ transition rate which, although relatively small, $\Delta_{01}^2 \ll \Delta_{12}^2$, acts to excite the qubit when the usually dominant $|1\rangle \longrightarrow |2\rangle$ transition rate vanishes. At low frequencies [$\nu \lesssim \nu_0 = (\Delta_{12}^3/A^*)^{1/2} \approx 10$ MHz], the state $|2\rangle$ is reached via adiabatic passage (Fig. 1B, red lines) and the population transfer and cooling become conveniently independent of detuning (see $\nu = 5$ MHz in Fig. 1C).

Maximal cooling occurs near an optimal driving amplitude (Fig. 2). Figure 2A shows the $|0\rangle$ state population P_{sw} measured as a function of the microwave amplitude A and flux detuning δf_q for frequency $\nu = 5$ MHz. The adiabatic passage regime, realized at this frequency, is particularly simple to interpret, although higher frequencies allow for an analogous interpretation. Cooling and the diamond feature of size $A^* = \varepsilon^*/2I_q$ can be understood in terms of the energy band diagram (Fig. 1B). For amplitudes $0 \le A \le A^*/2$, population transfer between states $|0\rangle$ and $|1\rangle$ occurs when $A > |\delta f_q|$, such that the sinusoidal flux reaches the Δ_{01} avoided crossing; this defines the front side of the observed spectroscopy diamond symmetric about the qubit step. For amplitudes $A^*/2 \le A \le A^*$, the Δ_{12} ($\Delta_{02'}$) avoided crossing dominates the dynamics, resulting in a second pair of thresholds $A = A^* - |\delta f_q|$, which define the back side of the diamond. As the diamond narrows to

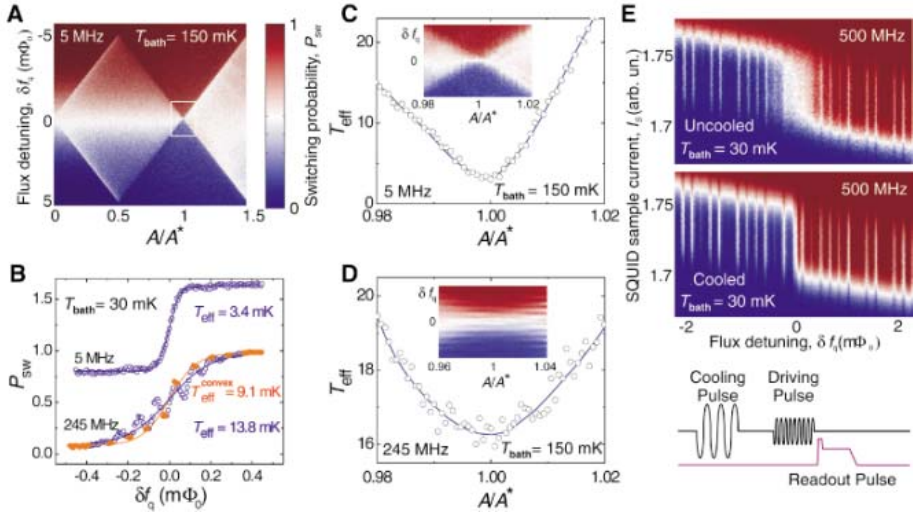

Fig. 2. Optimal cooling parameters and effective temperature. (**A**) State $|0\rangle$ population P_{sw} versus flux detuning, $-A^*/2 \lesssim \delta f_q \lesssim A^*/2$, and driving amplitude A with $\nu = 5$ MHz, $t_p = 3$ μs, and $T_{bath} = 150$ mK. Optimal conditions for cooling are realized at $A = A^*$, where A^* is defined in Fig. 1B. (**B**) Effective temperature T_{eff}. Qubit steps measured at $\nu = 5$ and 245 MHz (circles) and best fits to Eq. 2. At 245 MHz, the aggregate temperature fitting (blue, $T_{eff} = 13.8$ mK) and the convex fitting (orange, $T_{eff} = 9.1$ mK) are shown. $T_{bath} = 30$ mK. (**C** and **D**) (Inset) Detail of the region $A \approx A^*$ [white box in (A)] for $\nu = 5$ MHz (top) and $\nu = 245$ MHz (bottom). In each case, T_{eff} is extracted from the qubit step as in (B). Lines are guides for the eye; $t_p = 3$ μs, $T_{bath} = 150$ mK. (**E**) Spectroscopy of uncooled (top) and cooled (middle) qubit (5 MHz, 3-μs cooling pulse) at $T_{bath} = 30$ mK. Cumulative switching-probability distribution as a function of I_s and δf_q under 500-MHz ac excitation.

the point $A = A^*$, cooling is observed. There only one of the two side avoided crossings is reached and, thereby, strong transitions with relaxation to the ground state result for all δf_q, yielding the sharpest qubit step. For $A > A^*$, both side avoided crossings Δ_{12} and Δ_{02}, are reached simultaneously when $|\delta f_q| \lesssim A - A^*$, leading again to a large population transfer between $|0\rangle$ and $|1\rangle$.

When an ac field is applied, the qubit is no longer in equilibrium with the bath, but it can still be well characterized by an effective temperature T_{eff} using Eq. 2 with $T = T_{eff}$. This is illustrated in Fig. 2B for $\nu = 5$ MHz and $\nu = 245$ MHz ($T_{bath} = 30$ mK). At $\nu = 5$ MHz, the qubit step clearly follows Eq. 2, as shown with a fit line for $T_{eff} = 3.4$ mK. At 245 MHz, individual multiphoton resonances are evident, and P_{sw} is a nonmonotonic function of δf_q. In this case, T_{eff} is still a useful parameter to quantify the effective cooling, but it should be interpreted as an aggregate temperature over all frustrations. Alternatively, because the cooling is maximized at individual resonances, one may perform a convex fitting of Eq. 2, where only the solid (orange) symbols are taken into account to determine the effective temperature at the resonance detunings. The convex effective temperature $T_{eff}^{convex} = 9.1$ mK is smaller than the aggregate value $T_{eff} = 13.8$ mK. In the remainder of the paper, we refer to the more conservative effective temperature obtained using the aggregate definition.

Figure 2, C and D, show the variation of T_{eff} about $A = A^*$ for $\nu = 5$ MHz and $\nu = 245$ MHz, respectively, in the region marked with a white rectangle in Fig. 2A (insets show the raw data). As seen in these figures, T_{eff} typically presents a minimum, where the cooling is most efficient and from which A^* can be determined.

To determine whether the observation of a sharp qubit step proves that the system makes transitions to the ground state, as opposed to selectively populating an excited state with the same magnetization, we measured the excitation spectra of the "precooled" qubit and of the qubit in thermal equilibrium with the bath (Fig. 2E). In the former, a weak ac excitation was applied immediately after the cooling pulse (time lag less than 100 ns), well before the system equilibrates by warming up to the bath temperature (see below). By comparing the excitation spectra of the equilibrium and cooled systems (Fig. 2E, $T_{bath} = 30$ mK), we note that, although cooling markedly reduces the step width, making the qubit much colder, the excitation spectrum remains unchanged. Because the ac excitation is resonant with the $|0\rangle \rightarrow |1\rangle$ transition only, this strongly indicates that the population in a cooled qubit is in the ground state.

Figure 3, A and B, summarize the dependence of $T_{eff}^* = T_{eff}(A^*)$ on the dilution refrigerator temperature $T_{bath} = 30$ to 400 mK for several frequencies ν, spanning the resonant to the adiabatic passage limits, with a fixed pulse width $t_p = 3$ μs. In Fig. 3A, at large ν, T_{eff}^* exhibits a monotonic increase with T_{bath}, which becomes less pronounced as ν decreases. In the adiabatic passage limit, e.g., $\nu = 5$ MHz, $T_{eff}^* \approx 3$ mK is practically constant and reaches values that, notably, can be more than two orders of magnitude smaller than T_{bath}. In Fig. 3B, T_{eff}^* is observed to increase linearly with ν for different values of T_{bath}. Because the number of resonances in the qubit-step region is inversely proportional to ν, the cooling at the individual resonances depends only weakly on ν when using the convex definition $T_{eff}^{convex}(A^*)$.

Figure 3C displays the measurement-fidelity F versus T_{bath}. Although the qubit is effectively cooled, $T_{eff}^* \ll T_{bath}$, over the range of T_{bath} in Fig. 3, A and B, the readout SQUID is not actively cooled, and its switching current distribution broadens with T_{bath} (fig. S2). At high temperatures, the fidelity F, defined in Eq. 2, becomes too small to discriminate the two qubit states; this is independent of the qubit's effective temperature, which remains ~3 mK at all values of T_{bath}. We observe that the fidelity F is larger than 0.8 for $T_{bath} < 100$ mK, remains above 0.5 at ^{3}He refrigerator temperatures, but drops to $F \approx 0.1$ at $T_{bath} = 400$ mK, limiting our ability to measure the qubit state at higher temperatures (SOM Text).

The cooling and equilibration dynamics of the qubit are summarized in Fig. 4 ($T_{bath} = 150$ mK). Cooling a qubit in equilibrium with the bath requires a characteristic cooling time. In turn, a cooled qubit is effectively colder than its environment, a nonequilibrium condition, which over a characteristic equilibration time will thermalize to the environmental bath temperature. This relation between cooling and equilibration times determines the facility of cooling the qubit and performing operations while still cold. Figure 4, A and B, show the time evolution at cooling and warming up of the qubit step. The top panels show P_{sw} as a function of δf_q and cooling-pulse length t_p (Fig. 4A, $\nu = 245$ MHz), and as a function of δf_q and waiting-time t_w after

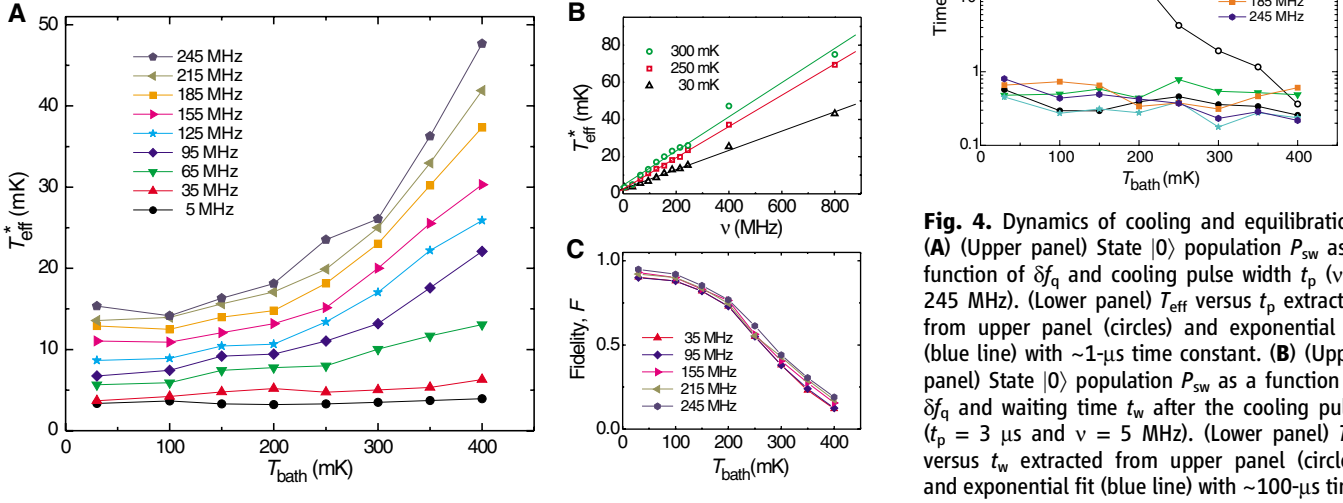

Fig. 4. Dynamics of cooling and equilibration. (**A**) (Upper panel) State $|0\rangle$ population P_{sw} as a function of δf_q and cooling pulse width t_p (ν = 245 MHz). (Lower panel) T_{eff} versus t_p extracted from upper panel (circles) and exponential fit (blue line) with ~1-μs time constant. (**B**) (Upper panel) State $|0\rangle$ population P_{sw} as a function of δf_q and waiting time t_w after the cooling pulse ($t_p = 3$ μs and $\nu = 5$ MHz). (Lower panel) T_{eff} versus t_w extracted from upper panel (circles) and exponential fit (blue line) with ~100-μs time constant. $T_{bath} = 150$ mK. (**C**) Characteristic equilibration and cooling times for different T_{bath}. Cooling is performed at the indicated frequencies.

Fig. 3. Effective temperature T_{eff}^* for $A = A^*$ and measurement fidelity F. (**A**) T_{eff}^* versus T_{bath} at the indicated driving frequencies ν. T_{eff}^* increases with T_{bath} at high ν, but remains constant at low ν. (**B**) T_{eff}^* versus ν for different values of T_{bath}. Lines are linear fits. (**C**) F versus T_{bath} at the indicated ν. A pulse width $t_p = 3$ μs was used in all cases.

precooling with a 5-MHz pulse (Fig. 4B) (for t_p and t_w definition, see fig. S1). Note the difference in the time scales, where it is observed that substantial cooling is accomplished within 1 μs (Fig. 4A), but equilibration occurs over a much longer time scale (Fig. 4B). Fitting to Eq. 2 yields T_{eff} as a function of t_p and t_w (Fig. 4, A and B, bottom panels). The near-exponential behavior of T_{eff} versus t_p and t_w allows one to infer the characteristic cooling and equilibration times as defined by an exponential fitting (solid blue lines), which are summarized in Fig. 4C. Notably, the cooling characteristic time is nearly independent of both ν and T_{bath} and, on average, is about 500 ns. In contrast, at the base temperature of the dilution refrigerator, the equilibration time is about three orders of magnitude longer, 300 μs, and remains one order of magnitude longer at 250 mK, a temperature that is accessible with ^{3}He refrigerators.

The minimum qubit effective temperature demonstrated in this work was estimated to be $T_{eff} \approx 3$ mK. This value is consistent with the inhomogeneously broadened linewidth observed in the experiment, which likely places a lower limit on the measurable minimum temperature. The microwave-induced cooling presented here can be applied to problems in quantum information science, including ancilla-qubit reset for quantum error-correcting codes and quantum-state preparation, with implications for improved fidelity and decoherence in multi-qubit systems. This approach, realized in a superconducting qubit, is generalizable to other solid-state qubits and can be used to cool other on-chip elements, e.g., the qubit circuitry or resonators.

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32. Materials and methods are available as supporting material on *Science* Online.
33. For negative δf_q, levels $|0\rangle$ and $|1\rangle$ exchange roles, and level $|2'\rangle$ plays the role of level $|2\rangle$. Unless explicitly noted, the discussions herein refer to positive δf_q.

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Supporting Online Material

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Materials and Methods
SOM Text
Figs. S1 and S2

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U-Pb Isotopic Age of the StW 573 Hominid from Sterkfontein, South Africa

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Sterkfontein cave, South Africa, has yielded an australopith skeleton, StW 573, whose completeness has excited great interest in paleoanthropology. StW 573, or "Little Foot," was found 25 meters below the surface in the Silberberg Grotto. ^{238}U-^{206}Pb measurements on speleothems immediately above and below the fossil remains, corrected for initial ^{234}U disequilibrium, yield ages of 2.17 ± 0.17 million years ago (Ma) and $2.24^{+0.09}_{-0.07}$ Ma, respectively, indicating an age for StW 573 of close to 2.2 Ma. This age is in contrast to an age of ~3.3 Ma suggested by magnetochronology and ages of ~4 Ma based on ^{10}Be and ^{26}Al, but it is compatible with a faunal age range of 4 to 2 Ma.

Sterkfontein, 50 km northwest of Johannesburg, is part of a world heritage site dubbed the Cradle of Humankind because it has produced about one-third of the world's known early hominid fossils (*1*). The Sterkfontein deposits formed in the lower levels of the pre-Cambrian Malmani dolomite (*2*) and are divided into stratigraphic members (members 1 to 6 from the base), correlating the deposits to a layer-cake stratigraphy (*3*, *4*). StW 573 comprises a skull, foot, tibia, radius, humerus, and other arm and hand bones (*5*, *6*). With its combination of human and ape-like features, this fossil has the potential to provide new insights into the evolution of early hominids, such as their degree of adaptation to bipedalism (*5*–*7*). The fossil is found within member 2 in the Silberberg Grotto, where the deposits comprise calcified breccias interlayered with flowstones, of which three flowstone layers are associated with StW 573 (Fig. 1). The skeleton is cemented in breccia on the flank of a former talus slope (*4*, *5*). The lower leg bones are separated from the remainder of the skeleton by part of flowstone layer 2C. This is due to partial slumping of the middle section of the skeleton before the formation of this flowstone (*5*). The flowstones are intact and show no signs of post-depositional faulting that would indicate later disturbance, and they are considered to lie in their original stratigraphic order.

Previous work on the age of StW 573 has been based on several types of evidence: fauna, stratigraphic position relative to an independently dated horizon, electron spin resonance (ESR), paleomagnetism, and cosmogenic isotopes. StW 573 was initially dated at 3.5 to 3.0 million years ago (Ma) according to the stratigraphic separation between members 2 and 4 (*7*, *8*) and the presence of a *Chasmaporthetes* specimen within the member 2 deposits (*6*) that was likened to a specimen at the Miocene-Pliocene site of Langebaanweg, South Africa (*9*). It was estimated that the intervening member 3 deposit, which is ~8 m in thickness (*10*), would have taken 300,000 to 500,000 years to accumulate (*7*, *8*). Member 4 was dated at 2.8 to 2.4 Ma through faunal correlation studies with dated East African assemblages (*11*–*13*) and at

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an average age of 2.1 ± 0.5 Ma by ESR (*14*). The member 4 hominid Sts 5 ("Mrs. Ples") is now considered to lie within the younger Reunion event at 2.15 to 2.14 Ma (*15*). An age range of 4.0 to 2.7 Ma, from fauna and stratigraphy, was used to fit the magnetic polarity record of flowstones; the result suggested an age of 3.58 to 3.22 Ma for StW 573, which was reduced to the narrower range of 3.33 to 3.30 Ma by interpolation of sedimentation rates (*4*). However, cosmogenic ^{26}Al and ^{10}Be burial dating of quartz in member 2 clastic sediments subsequently suggested an age of around 4 Ma (*16*). Although this is considerably older than the original suggested age of the reversal below StW 573, a Bayesian reanalysis of the cosmogenic data coupled with that magnetic reversal assigned the highest probability to an age of 4.29 Ma for the reversal (*17*). Despite the various dating techniques applied, controversy still surrounds the age of this fossil (*1*, *8*, *10*, *18*).

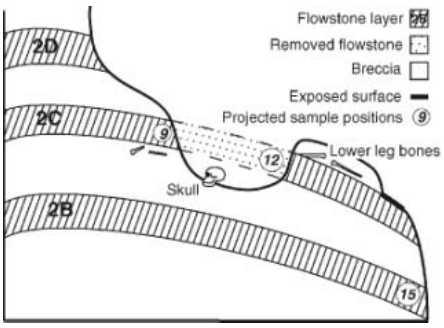

Fig. 1. Diagrammatic cross section of part of member 2 showing the relationship among flowstones, the fossil StW 573, and the positions of the new U-Pb samples [partly after (*5*)]. The bottom flowstone, 2B, is ~1 m below the skull. The middle flowstone, 2C, overlies the upper part of the skeleton but passes under the lower leg bones as a result of slumping before 2C formed. The top layer of flowstone, 2D, is ~1.5 m above the skull.

We used a method based on the accumulation of ^{206}Pb from the radioactive decay of ^{238}U. The potential of this approach has been demonstrated on young speleothems (<0.5 Ma) where U-Pb ages agreed with U-Th disequilibrium dates (*19*). The accumulation of radiogenic ^{206}Pb in young speleothems is influenced by two factors: (i) The discrimination against thorium during calcite crystallization results in a deficiency of radiogenic lead normally generated from ^{230}Th in secular equilibrium with ^{238}U, and (ii) the excess ^{234}U generally present in groundwater is incorporated along with ^{238}U in precipitated calcite, resulting in an excess of radiogenic ^{206}Pb; this will usually more than compensate for the first effect. ^{206}Pb-^{238}U ages calculated using the conventional age equation thus require a correction for ^{206}Pb produced from initial excess ^{234}U, otherwise the calculated age will be a maximum age (*20*). Typically, groundwater excess ^{234}U ranges up to 100%, although higher values occur. In the Transvaal dolomite, aquifer waters and younger speleothems with initial excess ^{234}U exceeding 1000% have been measured (*21*). Hence, ^{234}U/^{238}U ratios were measured to check whether residual disequilibrium was detectable and to establish limits on the extra ^{206}Pb generated from excess ^{234}U (*22*) (table S1).

We initially analyzed samples used for earlier paleomagnetic work (*4*) (SKA3, middle layer 2C). New hand specimens were also collected from the vicinity of the skeleton, three of which are shown schematically in Fig. 1: STA09, STA12, and STA15. Only samples with relatively high uranium concentrations and low initial

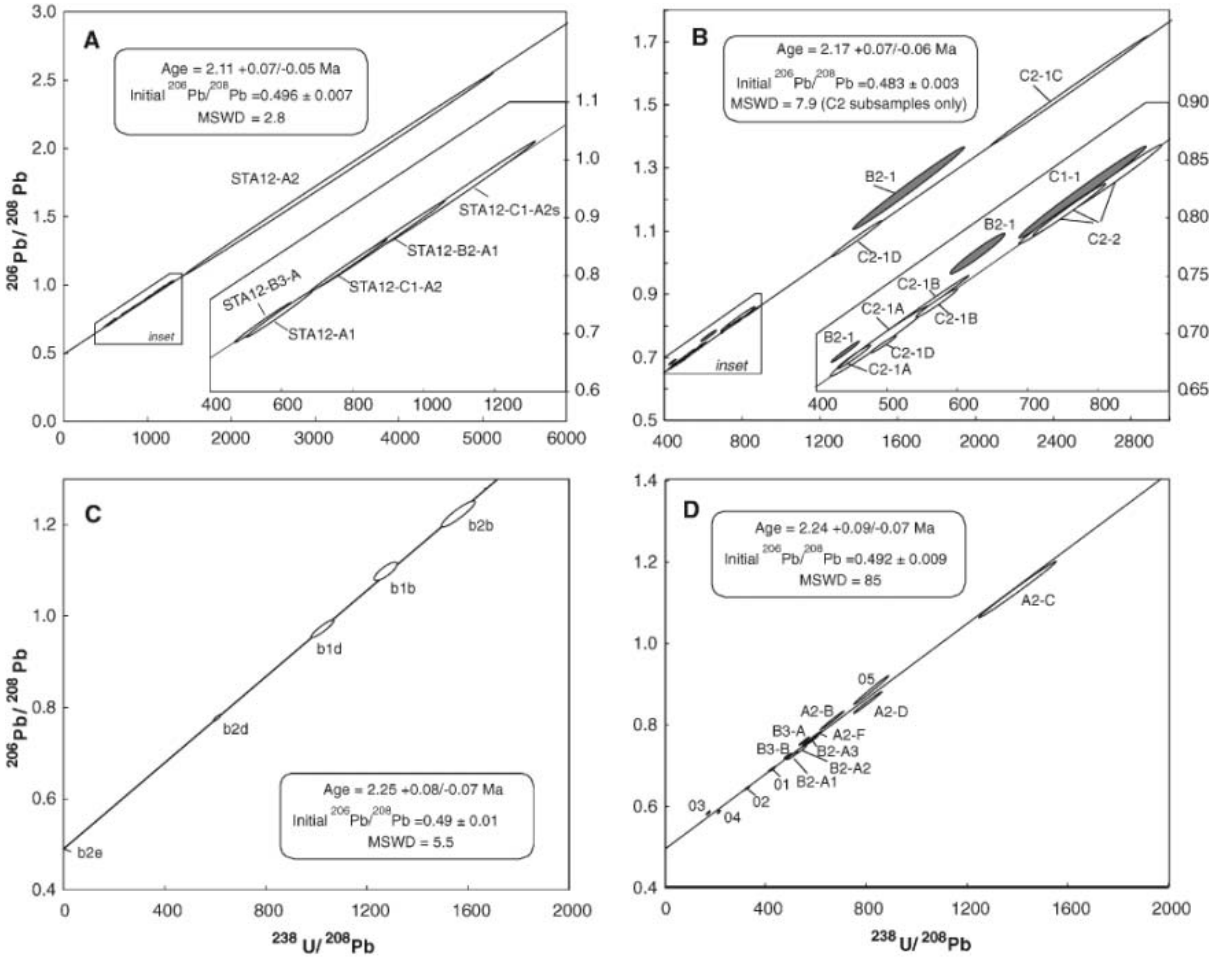

Fig. 2. Isotopic data: (**A**) STA12, (**B**) STA09, (**C**) SKA3 from flowstone layer 2C, (**D**) STA15 from flowstone 2B. The age values on the diagrams have been corrected for initial ^{234}U excess; the errors are estimated by quadratic combination of errors from this correction with errors on the isochron slope. See tables S1 and S2 for detailed data from the individual subsamples shown here.

(common) lead concentrations yielded statistically acceptable isochrons. The uranium concentrations varied from 0.3 to 1.4 ppm; lead concentrations were 0.45 to 10 ppb, corresponding to 0.2 to 4 ng. $^{238}U/^{208}Pb$ ratios ranged from 175 to 3135 (*22*) (table S1).

STA12 (Fig. 2A) has minimal excess scatter and an age of $2.11^{+0.07}_{-0.05}$ (2σ) Ma. STA09 (Fig. 2B) exhibits greater scatter, but the four closely spaced C2 subsamples yield a better defined line with mean square weighted deviation (MSWD) of 7.9, which gives an age of $2.17^{+0.07}_{-0.06}$ Ma. Subsamples from SKA3 (Fig. 2C) give a similar age of $2.25^{+0.08}_{-0.07}$ Ma. Combining the ages of these three samples from the middle layer 2C—which lie directly above StW 573—leads to an overall best estimate of 2.17 ± 0.17 Ma. The greater scatter in more widely spaced subsamples in STA09 probably reflects variable initial isotopic composition of lead or of uranium. Such variability is even more evident in STA15 (Fig. 2D) from the speleothem layer 2B below the skeleton, which has a high MSWD of 85. Nonetheless, when the data are regressed under the assumption that scatter is due to initial lead variation, the slope is well defined and yields a corrected age of $2.24^{+0.09}_{-0.07}$ Ma, similar to the age of the overlying speleothem.

The U-Pb data from flowstones 2C and 2B indicate an age for StW 573 of close to 2.2 Ma, which is considerably younger than other recent estimates including the original paleomagnetic age interpretations. In view of the new U-Pb dates, the short normal polarity recorded in the middle of layer 2C, with reversed polarity above and below, correlates in age with the younger Reunion event, which has global polarity time scale (GPTS) ages from 2.15 to 2.14 Ma (*23*) (Fig. 3). The next older normal event, Reunion 1, also appears to have been partly recorded in the top of layer 2B by samples 5 and 6: Our U-Pb age of 2.24 Ma closely matches 2.25 to 2.17 Ma, the revised ages (*24*, *25*) of the GPTS in (*23*). Thus, our age of around 2.2 Ma for StW 573 is compatible with the paleomagnetic record.

Our reasons for suggesting that these U-Pb ages may be preferable to estimates of an older age for StW 573 based on paleomagnetism or cosmogenic dating are as follows:

1) The U-Pb approach requires no assumptions about depositional history or about overall stratigraphy, and it is independent of previous chronological evidence.

2) The petrographic fabrics of the speleothem samples showed columnar palisade crystallites that are indicative of primary textures (*26*, *27*). Secondary recrystallized textures tend to have equant crystals (*27*).

3) The agreement in age among three samples from the same flowstone argues against extensive resetting, which would be highly unlikely to affect all samples to the same degree.

4) The cosmogenic age is dependent on a model in which aspects of the erosional and depositional history of the dated sediment must be assumed. In particular, it requires that the sediment reached its present position in the succession without any intermediate burial stage during which the ^{10}Be-^{26}Al system evolved before incorporation in the sampled breccia (*1*, *28*, *29*).

5) We have shown that the published paleomagnetic record is readily reconciled with the U-Pb ages derived above.

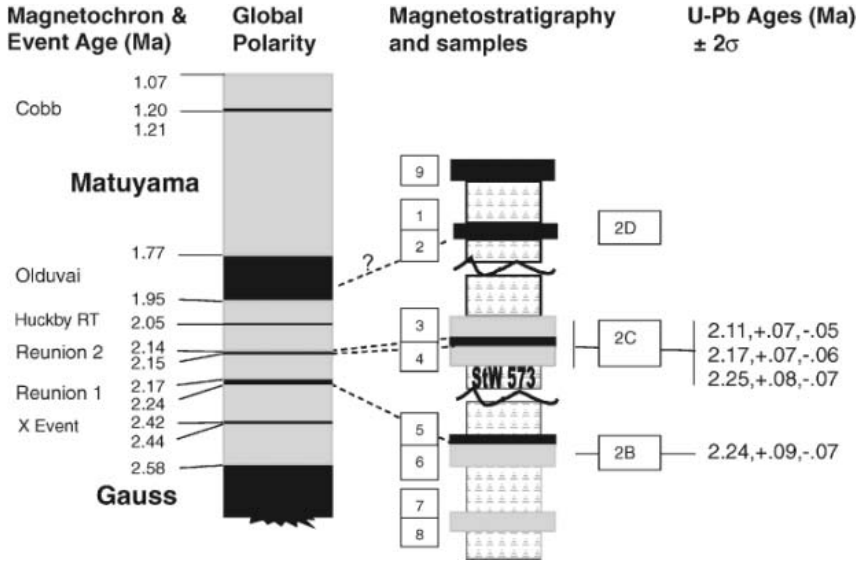

Fig. 3. Proposed reconciliation of the paleomagnetic data (*4*) with the magnetic polarity time scale (*23*–*25*) and the U-Pb ages of this study. For global polarities, black represents a normal Earth field and gray is reversed; Huckby RT, Huckleberry Ridge Tuff. Original paleomagnetic sample numbers are shown in small boxes against the magneto- and lithostratigraphy of member 2; 2B, 2C, and 2D are the submembers of member 2. The wide bars in the lithostratigraphy represent flowstones and the thinner bars represent calcite-indurated sediments and breccias. The wavy lines are possible hiatuses. U-Pb ages and age errors show that the recorded short normal events fit to Reunion 1 and Reunion 2 much better than to any other combination of short normals in this part of the Matuyama Chron.

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Supporting Online Material

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A Complex Oscillating Network of Signaling Genes Underlies the Mouse Segmentation Clock

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The segmental pattern of the spine is established early in development, when the vertebral precursors, the somites, are rhythmically produced from the presomitic mesoderm. Microarray studies of the mouse presomitic mesoderm transcriptome reveal that the oscillator associated with this process, the segmentation clock, drives the periodic expression of a large network of cyclic genes involved in cell signaling. Mutually exclusive activation of the notch–fibroblast growth factor and Wnt pathways during each cycle suggests that coordinated regulation of these three pathways underlies the clock oscillator.

The segmentation clock drives the expression of a very limited number of genes whose mRNA shows a dynamic expression sequence that is repeated in the presomitic mesoderm (PSM) each time a new somite forms (*1*). Most of the known cyclic genes are components of the notch pathway oscillating in phase with each other. In chick and mouse, they include genes coding for transcription factors of the hairy and enhancer of split (*Hes*) family and the lunatic fringe (*Lfng*) glycosyltransferase (*1*). Additionally, in mouse, a single component of the Wnt pathway, *Axin2*, oscillates out of phase with the notch pathway cyclic genes (*2*).

We have used gene expression arrays systematically to explore the cyclic transcription program associated with the segmentation clock in the mouse PSM. During the formation of each somite, *Lfng* is expressed in the PSM as a wave that sweeps across the tissue in a posterior-to-anterior direction (*1*). Therefore, by visually comparing the anteroposterior position of the *Lfng* expression stripes in the PSM in stained embryos, it is possible to define an approximate chronological order of the embryos along the segmentation clock oscillation cycle (*3*, *4*). We collected PSM samples from 40 mouse embryos ranging from 19 to 23 somites and used their *Lfng* expression patterns as a proxy to select 17 samples covering an entire oscillation cycle (fig. S1 and Figs. 1 and 2, A and B). Probes were produced from RNA extracted from the dissected PSMs by using a two-step amplification protocol and were hybridized to Affymetrix GeneChip MOE430A (Affymetrix, Santa Clara, CA) (*3*, *4*). The transcription profiles of known cyclic genes displayed pronounced patterns of oscillation (Fig. 2B). For example, the temporal pattern of *Hes1* expression detected on the arrays was in phase with the pattern of *Lfng* mRNA expression detected by in situ hybridization in the contralateral PSM (Fig. 2, A and B). This is expected because the mRNA of the notch pathway cyclic genes have been shown by in situ hybridization to oscillate synchronously in the PSM (*1*).

To identify genes displaying a periodic expression pattern in the PSM, we applied a recently developed modification of the Lomb-Scargle (L-S) algorithm (*3*, *4*) to the filtered data set. This allowed us to detect cyclic patterns characterized by different periods and to compute statistics that assess the significance of each periodic pattern. We operated under the assumption that the 17 samples were evenly spaced in time along the 2-hour segmentation clock cycle, resulting in a 7-min time interval between two consecutive time points (even though in reality the time points may not have been evenly spaced). This procedure allowed us to identify statistically significant periodic patterns along with their corresponding periods. The period with the most significant *P* value was selected for each profile. Six of the eight known mouse cyclic genes—*Hes1*, *Hes5*, *Hey1*, *Lfng*, *Axin2*, and *Nkd1*—were identified with periods of 94, 102, 112, 81, 102, and 112 min, respectively. These known cyclic genes were used as true positives to refine filtering parameters that minimize the number of candidate cyclic genes while maximizing the number of highly significant true positives among them. The most specific parameter settings retained 36 genes, including four of the known cyclic genes (table S2).

When ordered by their time of maximum expression in the segmentation clock cycle, identified cyclic genes segregate into two main clusters with opposite phase (Figs. 2C and 3, A to C). One of the clusters contains the known cyclic genes of the notch pathway–*Hes1*, *Hes5*, and *Hey1*–detected in this analysis (Fig. 2C).

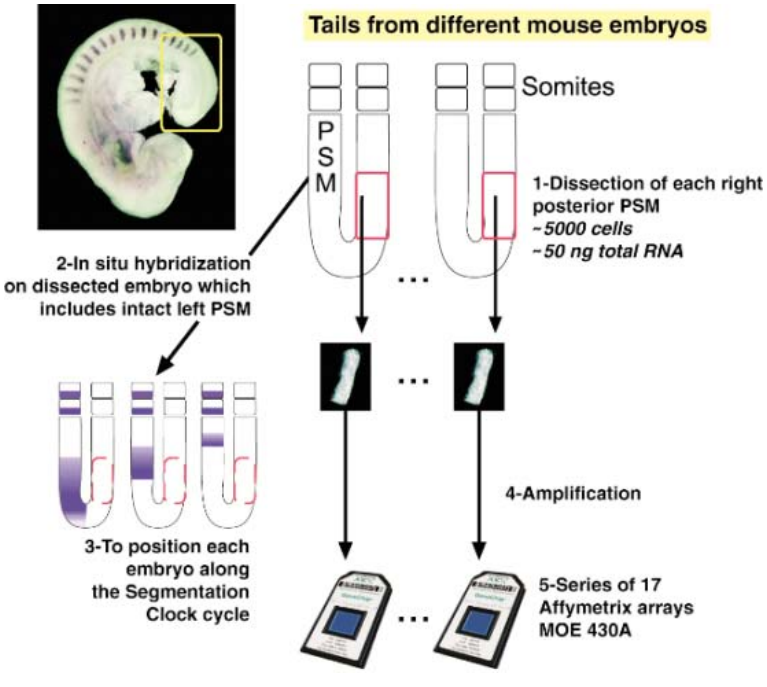

Fig. 1. Generation of a microarray time series of PSM samples along one period of the segmentation clock oscillation. (Top left image) Lateral view of a 9.0-day-postcoitus (dpc) mouse embryo labeled with *Uncx4.1*. Yellow box delimits the tail region, which contains the PSM schematized to the right. Schemes represent dorsal views of the tail region. The right posterior half PSM was dissected for the microarray analysis (red rectangle); the rest of the embryo including the intact left PSM was saved for in situ hybridization with *Lfng*. On the basis of the position of the *Lfng* stripes in the left PSM (purple), each sample could be positioned retrospectively along one period of the segmentation clock cycle.

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The basic helix-loop-helix (bHLH) transcription factor *Id1* that dimerizes with *Hes1* also belongs to this cluster (Fig. 2C) and exhibits a dynamic expression in the PSM (Fig. 3D). *Lfng* is also detected as periodic and in phase with the other notch cyclic genes, if slightly less stringent filtration parameters are used (Fig. 3A) (*3*, *4*). In addition, this cluster contains *Nrarp*, a direct target of notch signaling (Figs. 2C and 3A) (*5*). A clear *Nrarp* cyclic expression, reminiscent of *Lfng*, was observed after in situ hybridization in mouse embryos (Fig. 3E). A connection to Wnt signaling is provided by the vertebrate homolog of *legless*, *Bcl9L*, which shuttles β-catenin to the nucleus (Figs. 2C and 3A). Also, by using slightly less stringent thresholds (*3*, *4*), we find in this group *Nkd1* (Fig. 3A), an inhibitor of Wnt signaling acting downstream of notch in the segmentation clock (*6*).

The same cluster also contains genes coding for proteins involved in the fibroblast growth factor (FGF)–mitogen-activated protein kinase (MAPK) pathway, for example, the FGF pathway inhibitor *Spry2* (Figs. 2C and 3B) (*7*). With slightly less stringent filtration parameters, we also identified in this cluster another inhibitor of the FGF pathway, *Dusp6* (also called *Mkp3*), coding for an extracellular signal–regulated kinase (ERK) phosphatase (*8*) and the phosphatase *Shp2* (also called *Ptpn11*) required to activate the pathway (*3*, *4*) (Fig. 3B). Cyclic expression of *Spry2* and *Dusp6* was confirmed by in situ hybridization in the PSM (Fig. 3, F and G). Because *Spry2* and *Dusp6* expression was shown to be downstream of the FGF-MAPK pathway in the PSM of chick and mouse embryos (*8*, *9*), our data suggest that the FGF pathway is activated periodically in synchrony with the notch pathway in this tissue. Periodic expression of notch-related cyclic genes in the PSM is independent of FGF signaling (*9*, *10*). To test the possibility that the cyclic expression of FGF targets is imposed by periodic notch activation, we examined expression of *Spry2* in mice homozygous for a null allele of the *Rbpjk* gene, which abolishes notch signaling (*3*, *4*). In these mutants, *Spry2* expression remained dynamic (fig. S2, A and B, $n = 10$), suggesting that periodic expression of genes from notch and FGF pathways is activated in parallel. Other genes involved in FGF-MAPK signaling in this cluster include *Hspg2* (also called *Perlecan*) (Figs. 2C and 3B) (a coreceptor for FGF); the

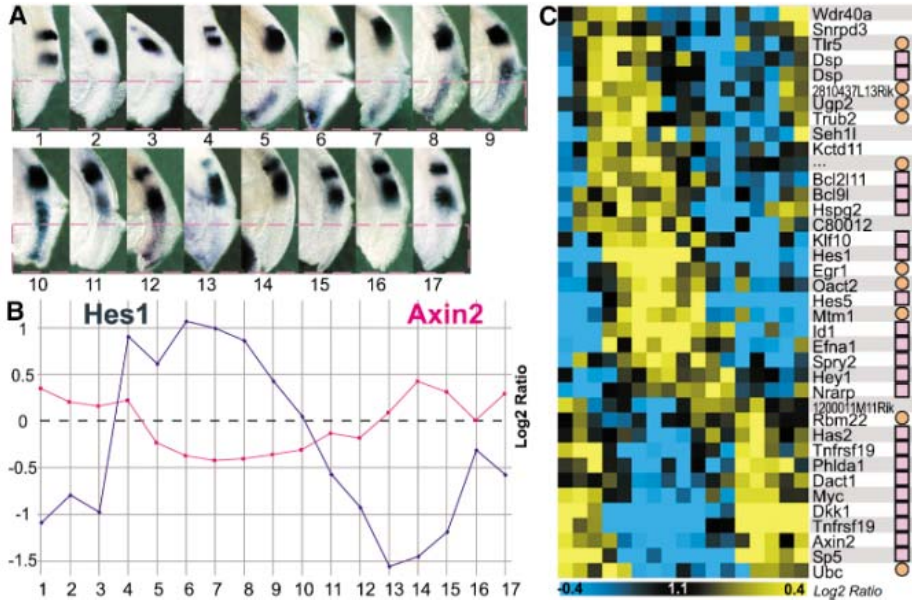

Fig. 2. Identification of cyclic genes based on the PSM microarray time series. (**A**) Left side of the 17 mouse embryos, whose right posterior PSMs (below red hatched line) were dissected for microarray analysis. Embryos were ordered along one segmentation clock cycle according to the position of *Lfng* stripes in their left PSM as revealed by in situ hybridization (fig. S1). (**B**) Log_2 ratios of the expression levels of the *Hes1* (blue) and *Axin2* (red) cyclic genes in each microarray of the time series. (**C**) Phaseogram of the cyclic genes identified by microarray and L-S analysis. Blue, decrease in gene expression; yellow, increase in gene expression; pink squares, genes validated by in situ hybridization; and orange circles, nonvalidated genes, that is, not evidently cyclical as detected by in situ hybridization.

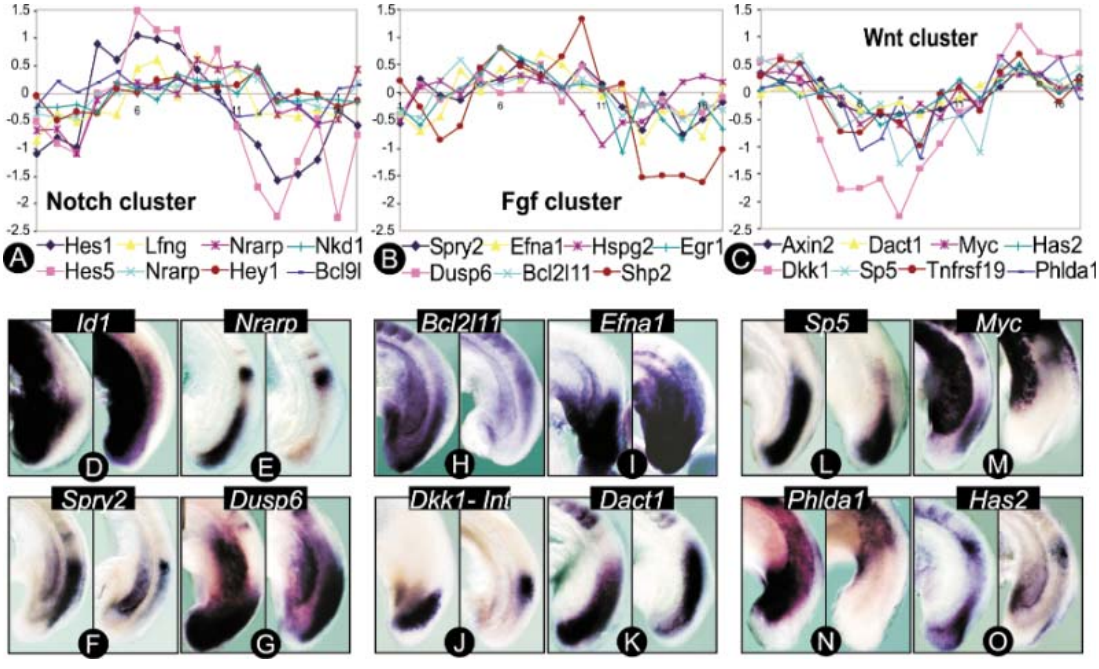

Fig. 3. Mutually exclusive activation of the notch-FGF and Wnt clusters during one segmentation clock oscillation. Expression profiles of cyclic genes of (**A**) notch, (**B**) FGF, and (**C**) Wnt pathways along the microarray time series. (**D** to **O**) Lateral view of the right caudal part of 9.0-dpc mouse embryos hybridized with the probes indicated in black boxes. For each probe, two representative images illustrating the dynamic expression of the gene in the PSM are shown.

Bcl2-family member *Bcl2l11* (also called *Bim*) (Figs. 2C and 3, B and H) and the Zn finger transcription factor Egr1 (Figs. 2C and 3B), which act downstream of the MAPK pathway; and *EphrinA1* (*efna1*) (Figs. 2C and 3, B and I). Because it has been proposed that FGF and Wnt signaling establish a dynamic gradient that controls the competence of PSM cells to respond to the segmentation clock (*2*, *10*), our data point to a further degree of complexity regulating FGF signaling in the PSM.

The second cluster of periodic genes contains genes cycling in opposite phase to the notch-FGF cluster (Figs. 2C and 3C). In this cluster, we found the known cyclic gene *Axin2* and a majority of the cyclic genes associated with Wnt signaling (Fig. 3C). These include the soluble Wnt inhibitor Dkk1 and the intracellular Wnt inhibitor binding to dishevelled, Dact1 (also known as Dpr or Frodo). Other genes in this cluster, such as those coding for the transcription factors Sp5 and c-Myc and the transmembrane receptor Tnfrsf19 (also called *Troy*), are downstream targets of the Wnt pathway (*11*–*13*). Two other genes in this cluster, the hyaluronan synthase *Has2* (*14*) and the *Phlda1* gene involved in Fas signaling (*15*), have no known association with the Wnt pathway. Their expression is strongly down-regulated in *Wnt3a* hypomorph mouse mutants *vestigial tail* (*vt*), suggesting that these genes are also targets of Wnt signaling (fig. S2, C to F). All of these genes show a dynamic expression pattern in the PSM with the use of in situ hybridization (Fig. 3, J to O, and fig. S3). Inactivation of *Dkk1* (*16*), *Sp5* (*17*), *c-Myc* (*18*), and *has2* (*14*) has been reported to produce segmentation defects. Dynamic expression of *Dkk1* was observed by in situ hybridization only when we used intronic probes that recognize nascent nuclear transcripts (Fig. 3J). This suggests that *Dkk1* is periodically transcribed in the PSM but that its mRNA is too stable to allow visualization of its oscillations by in situ detection using a probe recognizing the cytoplasmic mRNA transcripts. This could essentially reflect different sensitivity ranges between the microarray and the in situ hybridization methods.

The majority of the cyclic genes from the Wnt cluster, including *Dkk1*, *c-Myc*, *Axin2*, *Sp5*, and *Tnfrsf19*, are direct downstream targets of the Wnt pathway (*11*–*13*, *19*, *20*), suggesting that the Wnt pathway is rhythmically activated in the PSM. Recent gene expression analysis in the mouse embryo identified a much larger number of downstream targets of Wnt signaling than the set of genes coregulated with *Axin2* (*21*, *22*). The only common gene between these embryonic Wnt targets and the cyclic genes identified by L-S analysis was *Axin2*. Thus, Wnt pathway genes periodically transcribed in the PSM appear to involve a restricted subset of the Wnt target genes.

Genes in the notch–FGF, and Wnt clusters identified by our approach are expressed in opposite phases during each segmentation clock cycle (Fig. 4), suggesting that, whereas notch and FGF might act synergistically, their activation is mutually exclusive to that of the Wnt pathway in the PSM. This is consistent with the idea that reciprocal inhibition of notch-FGF and Wnt pathways might play a role in the implementation of the clock oscillations.

Cyclic expression of 20 out of 29 tested genes (69%) was validated by in situ hybridization, demonstrating the high efficiency of our strategy to identify cyclic genes (Fig. 2C). This number is most likely an underestimation of the total number of bona fide cyclic genes, which is expected to increase with the use of arrays covering a larger fraction of mouse genes, with improved amplification techniques, and with better sampling allowing more robust signal detection. Therefore, we expect a minimum number of cyclic genes between 50 and 100. Most of the validated cyclic genes we identified are involved in signal transduction or transcription and belong to the notch, Wnt, and FGF pathways, suggesting that the oscillator mechanism largely relies on these three pathways. In the yeast cell cycle, periodic transcriptional regulation is restricted to selected (perhaps limiting) subunits of multiprotein complexes that control the cycle (*23*). Similarly in the segmentation clock, only a subset of the components of the notch, FGF, and Wnt pathways are expressed in a periodic fashion, at least at the mRNA level. The half-life of proteins coded by the cyclic genes *Hes1*, *Hes7*, and *Lfng* has been shown to be very short (*1*), hence leading to protein oscillations with the same period as their mRNAs. It is expected that an important number of the identified cyclic genes encode cyclic proteins that could act in the oscillator mechanism. Thus, a model of dynamic complex assembly may also control the periodic signaling associated with the segmentation clock network.

Current models of the segmentation clock have their basis in a very limited number of inhibitory components that establish negative feedback loops involved in the generation of oscillations (*1*). Our analysis identified several additional inhibitors of the notch, FGF, and Wnt pathways that could, in principle, participate in similar negative feedback loops. Thus, our data suggest that the oscillator relies on the periodic regulation of a network of such inhibitors rather than on a few key components. Such a network might account for the robustness of the segmentation process.

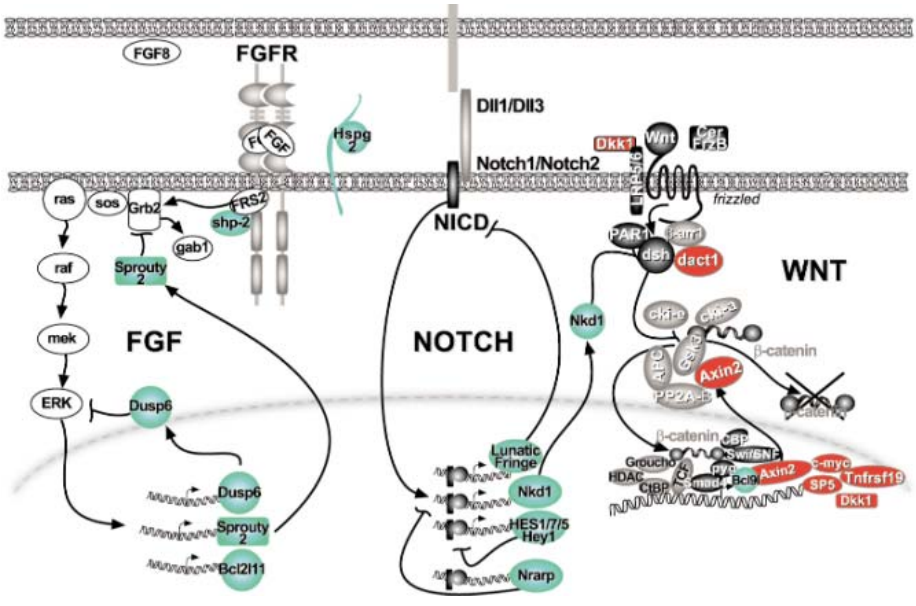

Fig. 4. A network of cyclic genes of the notch, FGF, and Wnt pathways underlies the mouse segmentation clock. Notch and FGF-MAPK cyclic genes (green) oscillate in opposite phase to Wnt cyclic genes (red). The other components (black and white) belong to the canonical notch, FGF-MAPK, and Wnt pathways. A large number of identified cyclic genes are involved in negative feedback loops.

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Carbon-Negative Biofuels from Low-Input High-Diversity Grassland Biomass

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Biofuels derived from low-input high-diversity (LIHD) mixtures of native grassland perennials can provide more usable energy, greater greenhouse gas reductions, and less agrichemical pollution per hectare than can corn grain ethanol or soybean biodiesel. High-diversity grasslands had increasingly higher bioenergy yields that were 238% greater than monoculture yields after a decade. LIHD biofuels are carbon negative because net ecosystem carbon dioxide sequestration (4.4 megagram hectare^{-1} year^{-1} of carbon dioxide in soil and roots) exceeds fossil carbon dioxide release during biofuel production (0.32 megagram hectare^{-1} year^{-1}). Moreover, LIHD biofuels can be produced on agriculturally degraded lands and thus need to neither displace food production nor cause loss of biodiversity via habitat destruction.

Globally escalating demands for both food (*1*) and energy (*2*) have raised concerns about the potential for food-based biofuels to be sustainable, abundant, and environmentally beneficial energy sources. Current biofuel production competes for fertile land with food production, increases pollution from fertilizers and pesticides, and threatens biodiversity when natural lands are converted to biofuel production. The two major classes of biomass for biofuel production recognized to date are monoculture crops grown on fertile soils (such as corn, soybeans, oilseed rape, switchgrass, sugarcane, willow, and hybrid poplar) (*3*–*6*) and waste biomass (such as straw, corn stover, and waste wood) (*7*–*9*). Here, we show the potential for a third major source of biofuel biomass, high-diversity mixtures of plants grown with low inputs on agriculturally degraded land, to address such concerns.

We performed an experiment on agriculturally degraded and abandoned nitrogen-poor sandy soil. We determined bioenergy production and ecosystem carbon sequestration in 152 plots, planted in 1994, containing various combinations of 1, 2, 4, 8, or 16 perennial herbaceous grassland species (table S1) (*10*). Species composition of each plot was determined by random draw from a pool of species. Plots were unfertilized, irrigated only during establishment, and otherwise grown with low inputs (*10*). The 16-species plots are the highest diversity, or the LIHD (low-input, high-diversity), treatment. All plots were burned in early spring to remove aboveground biomass before growth began. Soil samples, collected before planting in 1994 and again in 2004, determined carbon sequestration in soil. Plots were sampled annually from 1996 to 2005 for aboveground biomass production.

Annual production of aboveground bioenergy (i.e., biomass yield multiplied by energy released upon combustion) (*10*) was an approximate log function of planted species number (Fig. 1A). On average for the last 3 years of the experiment (2003–2005), 2-, 4-, 8-, and 16-species plots produced 84%, 100%, 157%, and 238% more bioenergy, respectively, than did plots planted with single species. In a repeated measures multivariate analysis of variance, annual bioenergy production was positively dependent on the number of planted species ($F_{1,\ 155} = 68.4$, $P < 0.0001$), on time ($F_{9,\ 147} = 8.81$, $P < 0.0001$), and on a positive time-by-species number interaction ($F_{9,\ 147} = 11.3$, $P < 0.0001$). The interaction occurred because bioenergy production increased more through time in LIHD treatments than in monocultures and low-diversity treatments, as shown by the ratio of bioenergy in LIHD (16 species) plots to those in 8-, 4-, 2-, and 1-species plots (Fig. 1B).

The gross bioenergy yield from LIHD plots was 68.1 GJ ha^{-1} year^{-1}. Fossil energy needed for biomass production, harvest, and transport to a biofuel production facility was estimated at 4.0 GJ ha^{-1} year^{-1} (table S2). Different biofuel production methods capture different proportions of bioenergy in deliverable, usable forms (Fig. 2) (*10*). Cocombustion of degraded land LIHD biomass with coal in existing coal-fired electric generation facilities would provide a net gain of about 18.1 GJ ha^{-1} as electricity (*11*). Converting LIHD biomass into cellulosic ethanol and electricity is estimated to net 17.8 GJ ha^{-1} (*12*). Conversion into gasoline and diesel synfuels and electricity via integrated gasification and combined cycle technology with Fischer-Tropsch hydrocarbon synthesis (IGCC-FT) is estimated to net 28.4 GJ ha^{-1} (*10*, *13*). In contrast, net energy gains from corn and soybeans from fertile agricultural soils are 18.8 GJ ha^{-1} for corn grain ethanol and 14.4 GJ ha^{-1} for soybean biodiesel (*14*). Thus, LIHD biomass converted via IGCC-FT yields 51% more usable energy per hectare from degraded infertile land than does corn grain ethanol from fertile soils. This higher net energy gain results from (i) low-energy inputs in LIHD biomass production because the crop is perennial and is neither cultivated, treated with herbicides, nor irrigated once established and likely requires only phosphorus replacement fertilization because nitrogen is provided by legumes; (ii) the more than 200% higher bioenergy yield associated with high crop biodiversity; and (iii) the use of all aboveground biomass, rather than just seed, for energy. LIHD biofuels also provide much greater net energy outputs per unit of fossil fuel input than do current biofuels [net energy balance (NEB) ratios of Fig. 2]. Fertile lands yield about 50% more LIHD biomass (and bioenergy) than our degraded soils (*15*, *16*).

Annual carbon storage in soil was a log function of plant species number (Fig. 1C). For 1994–2004, there was no significant net sequestration of atmospheric CO_2 in monoculture plots [mean net release of CO_2 of 0.48 ± 0.44 Mg ha^{-1} year^{-1} (mean ± SE)], but, in LIHD plots, there was significant soil sequestration of CO_2 (2.7 ± 0.29 Mg ha^{-1} year^{-1}). Soil carbon storage occurred even though all aboveground biomass-based organic matter was removed annually via burning. Periodic resampling of soils in a series of prairie-like agriculturally degraded fields found C storage rates similar to those of the LIHD treatment and suggested that this rate could be maintained for a century (*17*). The observed annual rate of change in soil C at a particular soil depth declined with depth ($P = 0.035$), suggesting that an additional 5% more

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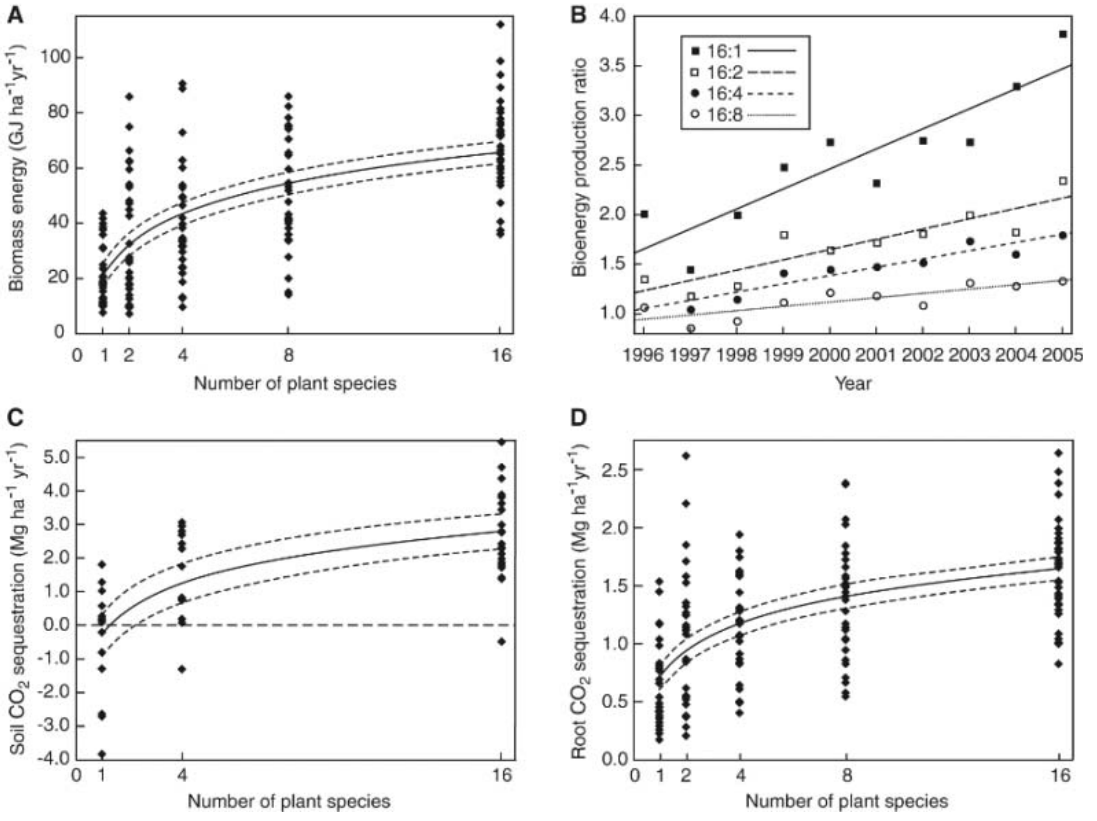

Fig. 1. Effects of plant diversity on biomass energy yield and CO_2 sequestration for low-input perennial grasslands. (**A**) Gross energy content of harvested aboveground biomass (2003–2005 plot averages) increases with plant species number. (**B**) Ratio of mean biomass energy production of 16-species (LIHD) treatment to means of each lower diversity treatment. Diverse plots became increasingly more productive over time. (**C**) Annual net increase in soil organic carbon (expressed as mass of CO_2 sequestered in upper 60 cm of soil) increases with plant diversity as does (**D**) annual net sequestration of atmospheric carbon (as mass of CO_2) in roots of perennial plant species. Solid curved lines are log fits; dashed curved lines give 95% confidence intervals for these fits.

C may be stored in soils deeper than we measured (below 60 cm depth).

In 2004, after 10 years of growth, atmospheric CO_2 sequestration in roots was a log function of plant species numbers (Fig. 1D). On an annual basis, 0.62 Mg ha^{-1} year^{-1} of atmospheric CO_2 was sequestered in roots of species grown in monocultures, and 160% more CO_2 (1.7 Mg ha^{-1} year^{-1}) was captured in roots of 16-species plots. Multiple regression showed that root CO_2 sequestration (Mg ha^{-1} of CO_2) increased as a log function of plant species number (S), as a log function of time ($Year$), and their interaction $\{C_{root} = -1.47 + 6.16\log_{10}(S) + 9.64\log_{10}(Year) + 9.60[\log_{10}(S) - 0.613][\log_{10}(Year) - 0.782]$ where $Year = 3$ for 1997, the first time roots were sampled; overall $F_{3,\ 1260} = 191$, $P < 0.0001$; for $\log_{10}(S)$, $F_{1,\ 1260} = 398$, $P < 0.0001$; for $Year$, $F_{1,\ 1260} = 148$, $P = 0.0001$; for $S \times Year$, $F_{1,\ 1260} = 27.3$, $P = 0.0001\}$. This regression suggests that most root carbon storage occurred in the first decade of growth; during the second decade, roots of 16-species plots are projected to store just 22% of C stored during the first decade. Measurements at greater depths in 10 LIHD plots suggest that 43% more C may be stored in roots between 30 and 100 cm.

LIHD plots had a total CO_2 sequestration rate of 4.4 Mg ha^{-1} year^{-1} in soil and roots during the decade of observation. Trends suggest that this rate might decline to about 3.3 Mg ha^{-1} year^{-1} during the second decade because of slower root mass accumulation. In contrast, the annual rate of CO_2 sequestration for monocultures was 0.14 Mg ha^{-1} year^{-1} for the first decade and projected to be indistinguishable from zero for subsequent decades.

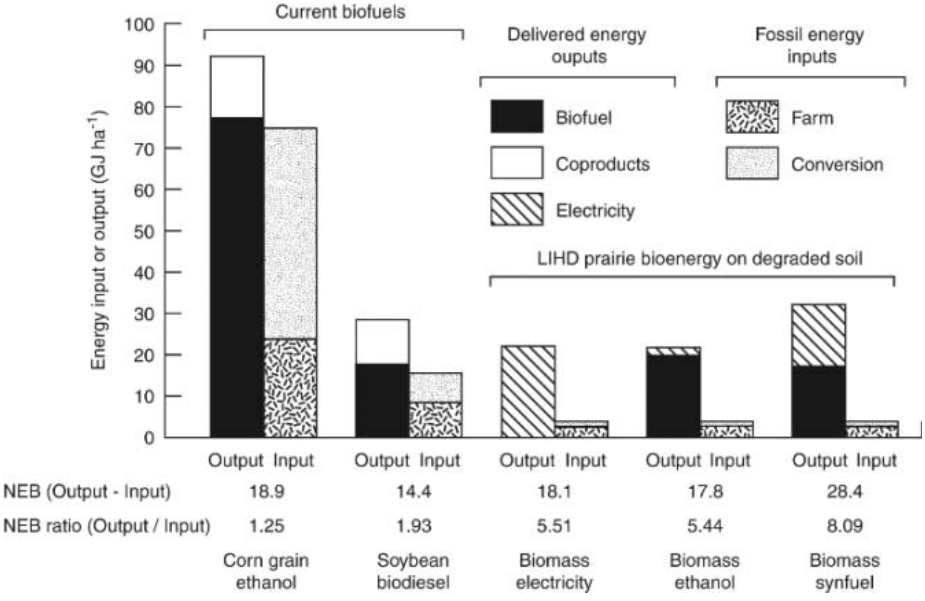

Fig. 2. NEB for two food-based biofuels (current biofuels) grown on fertile soils and for LIHD biofuels from agriculturally degraded soil. NEB is the sum of all energy outputs (including coproducts) minus the sum of fossil energy inputs. NEB ratio is the sum of energy outputs divided by the sum of fossil energy inputs. Estimates for corn grain ethanol and soybean biodiesel are from (*14*).

Across their full life cycles, biofuels can be carbon neutral [no net effect on atmospheric CO_2 and other greenhouse gases (GHG)], carbon negative (net reduction in GHG), or carbon sources (net increase in GHG), depending on both how much CO_2 and other greenhouse gases, expressed as CO_2 equivalents, are removed from or released into the atmosphere

during crop growth and how much fossil CO_2 is released in biofuel production. Both corn ethanol and soybean biodiesel are net carbon sources but do have 12% and 41% lower net GHG emissions, respectively, than combustion of the gasoline and diesel they displace (*14*). In contrast, LIHD biofuels are carbon negative, leading to net sequestration of atmospheric CO_2 across the full life cycle of biofuel production and combustion (table S3). LIHD biomass removed and sequestered more atmospheric CO_2 than was released from fossil fuel combustion during agriculture, transportation, and processing (0.32 Mg ha^{-1} year^{-1} of CO_2), with net life cycle sequestration of 4.1 Mg ha^{-1} year^{-1} of CO_2 for the first decade and an estimated 2.7 to 3 Mg ha^{-1} year^{-1} for subsequent decades. GHG reductions from use of LIHD biofuels in lieu of gasoline and diesel fuel are from 6 to 16 times greater than those from use of corn grain ethanol and soybean biodiesel in lieu of fossil fuels (Fig. 3A).

LIHD biofuel production should be sustainable with low inputs of agrichemicals, as in our study. Legumes in LIHD plots can supply nitrogen (*18*). In our experiment, total soil nitrogen of LIHD plots increased 24.5% ($P < 0.001$) from 1994–2004, but monoculture total soil nitrogen was unchanged ($P = 0.83$). However, some amount of N fertilization may be useful in dry habitats that lack efficient N-fixing species. Application of P or other nutrients may be needed if initially limiting or to replace nutrient exports (Fig. 3B). Production may be sustainable with low pesticide use, because plant disease incidence and invasion by exotic species are low in high-diversity plant mixtures (Fig. 3C) (*19*).

Switchgrass (*Panicum virgatum*), which is being developed as a perennial bioenergy crop, was included in our experiment. Switchgrass monocultures can be highly productive on fertile soils, especially with application of pesticides and fertilizer (*20*, *21*). However, on our infertile soils, switchgrass monoculture bioenergy [23.0 ± 2.4 GJ ha^{-1} year^{-1} (mean ± SE)] was indistinguishable from mean bioenergy of monocultures of all other species (22.7 ± 2.7 GJ ha^{-1} year^{-1}) and yielded just a third of the energy of LIHD plots (*10*).

How much energy might LIHD biomass potentially provide? For a rough global estimate, consider that about 5×10^8 ha of agriculturally abandoned and degraded land producing biomass at 90 GJ ha^{-1} year^{-1} (*22*) could provide, via IGCC-FT, about 13% of global petroleum consumption for transportation and 19% of global electricity consumption (*2*). Without accounting for ecosystem CO_2 sequestration, this could eliminate 15% of current global CO_2 emissions, providing one of seven CO_2 reduction "wedges" needed to stabilize global CO_2 (*23*). GHG benefits would be larger if LIHD biofuels were, in general, carbon negative, as might be expected if late-successional native plant species were used in LIHD biomass production on degraded soils [e.g., (*17*)].

The doubling of global demand for food and energy predicted for the coming 50 years (*1*, *2*) and the accelerating use of food crops for biofuels have raised concerns about biodiversity loss if extant native ecosystems are converted to meet demand for both food and biofuels. There are also concerns about environmental impacts of agrichemical pollution from biofuel production and about climate change from fossil fuel combustion (*14*, *24*–*26*). Because LIHD biomass can be produced on abandoned agricultural lands, LIHD biofuels need neither compete for fertile soils with food production nor encourage ecosystem destruction. LIHD biomass can produce carbon-negative biofuels and can reduce agrichemical use compared with food-based biofuels. Moreover, LIHD ecosystem management may provide other ecosystem services, including stable production of energy, renewal of soil fertility, cleaner ground and surface waters, wildlife habitat, and recreation (*18*, *19*, *24*, *27*, *28*). We suggest that the potential for biofuel production and carbon sequestration via low inputs and high plant diversity be explored more widely.

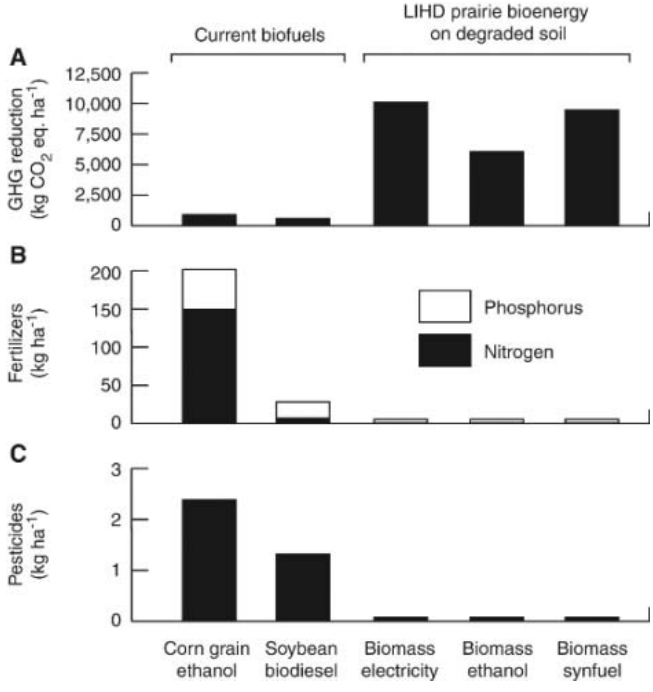

Fig. 3. Environmental effects of bioenergy sources. (**A**) GHG reduction for complete life cycles from biofuel production through combustion, representing reduction relative to emissions from combustion of fossil fuels for which a biofuel substitutes. (**B**) Fertilizer and (**C**) pesticide application rates are U.S. averages for corn and soybeans (*29*). For LIHD biomass, application rates are based on analyses of table S2 (*10*).

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Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5805/1598/DC1
Materials and Methods
Tables S1 to S3
References

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Synthesis-Mediated Release of a Small RNA Inhibitor of RNA Polymerase

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Noncoding small RNAs regulate gene expression in all organisms, in some cases through direct association with RNA polymerase (RNAP). Here we report that the mechanism of 6*S* RNA inhibition of transcription is through specific, stable interactions with the active site of *Escherichia coli* RNAP that exclude promoter DNA binding. In fact, the DNA-dependent RNAP uses bound 6*S* RNA as a template for RNA synthesis, producing 14- to 20-nucleotide RNA products (pRNA). These results demonstrate that 6*S* RNA is functionally engaged in the active site of RNAP. Synthesis of pRNA destabilizes 6*S* RNA–RNAP complexes leading to release of the pRNA-6*S* RNA hybrid. In vivo, 6*S* RNA–directed RNA synthesis occurs during outgrowth from the stationary phase and likely is responsible for liberating RNAP from 6*S* RNA in response to nutrient availability.

The majority of noncoding small RNAs (sRNAs) of known function act by forming base pairs with target mRNAs, thereby altering translation or mRNA stability (*1*–*3*). However, bacterial and eukaryotic RNAs exist that alter gene expression by binding directly to RNA polymerase (RNAP) (*1*, *4*). The bacterial 6*S* RNA mediates cellular response to environmental stresses in *Escherichia coli* when nutrients are limiting (*5*, *6*). This highly conserved RNA forms a specific, stable complex with the σ^{70}-containing form of RNAP ($E\sigma^{70}$), inhibiting transcription at many, although not all, σ^{70}-dependent promoters (*5*, *7*, *8*). The murine B2 RNA, unrelated to 6*S* RNA in sequence and structure, has been shown to down-regulate transcription during heat shock. B2 RNA binds RNAP II and blocks isomerization steps that occur during transcription initiation after promoter binding (*4*). A crystal structure of a synthetic RNA (FC*) postulated to act similarly to B2, revealed that it binds near the active site of yeast RNAP II (*9*).

The conserved secondary structure of 6*S* RNA is critical for function and features a large, single-stranded bulge within a mostly double-stranded molecule (Fig. 1A) (*8*, *10*). The similarity of this structure to the melted DNA conformation in the "open complex" formed during transcription initiation suggests that 6*S* RNA inhibits transcription by competing with promoter DNA binding. To test this hypothesis, $E\sigma^{70}$ binding to a DNA promoter was examined in the presence or absence of 6*S* RNA (*11*). $E\sigma^{70}$ efficiently bound to duplex DNA containing a consensus promoter (*12*). Preincubation of 6*S* RNA with $E\sigma^{70}$ significantly reduced DNA binding, whereas an inactive mutant 6*S* RNA lacking most of the single-stranded region (M5) (*8*) had no detectable effect (Fig. 1C). Furthermore, 6*S* RNA strongly reduced binding of a single-stranded DNA oligonucleotide that mimics the specific interactions between $E\sigma^{70}$ and the nontemplate strand within the open complex (*12*–*14*), whereas the M5 control did not (Fig. 1D). These results indicate that 6*S* RNA inhibits transcription by blocking DNA binding, in contrast to B2 and FC* RNAs, which inhibit transcription at a later step in initiation (*4*).

To determine whether 6*S* RNA is near the active site of RNAP. 6*S* RNA:$E\sigma^{70}$ complexes were incubated with ammonium Fe(II) sulfate. Fe^{2+} can replace Mg^{2+} in the active site of RNAP and can generate localized hydroxyl radicals that cleave biopolymer chains within ~10 Å (*15*). 6*S*, but not the inactive M5, RNA was cleaved in the presence of iron (fig. S1). Cleavage was strongest at U44 and A43 of 6*S* RNA and weaker at neighboring A45, U46, and G42 residues (see Fig. 1A).

The iron-directed cleavage sites are located within the "bubble" region of 6*S* RNA and orient 6*S* RNA relative to $E\sigma^{70}$. The position of the active site within the bubble appears analogous to where transcription initiates in the open complex formed with promoter DNA (see Fig. 1). This similarity prompted us to test whether 6*S* RNA could act as a template for RNA synthesis. Initiation of RNA synthesis can be detected by examining the addition of a single templated nucleotide (corresponding to the +3 position) to a dinucleotide complementary to positions +1 and +2 on the template. 6*S* RNA directs the addition of cytidine 5′-triphosphate (CTP), but not guanosine 5′-triphosphate (GTP), to ApU (Fig. 2A and fig. S2). No products were observed in the absence of an RNA template, from the M5 control, or from using ApC to initiate synthesis; this shows that specific RNA synthesis occurs. Tem-

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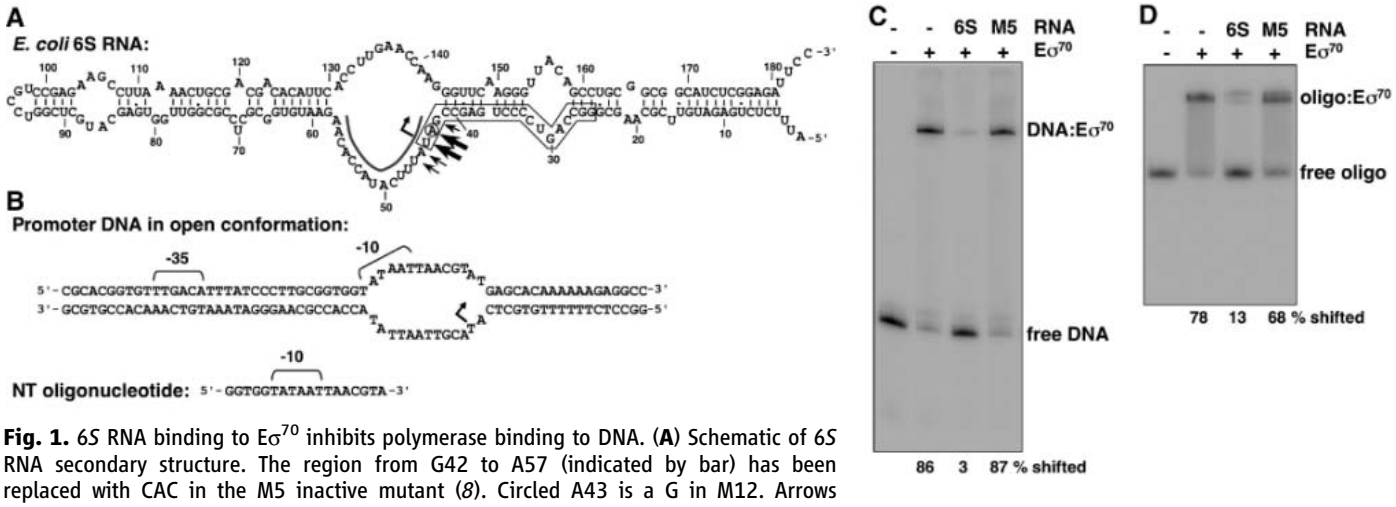

Fig. 1. 6*S* RNA binding to $E\sigma^{70}$ inhibits polymerase binding to DNA. (**A**) Schematic of 6*S* RNA secondary structure. The region from G42 to A57 (indicated by bar) has been replaced with CAC in the M5 inactive mutant (*8*). Circled A43 is a G in M12. Arrows indicate iron cleavage sites (see fig. S1). The sequence in 6*S* RNA complementary to the longest pRNA is boxed (see Fig. 2B). (**B**) Sequences of DNA promoter and nontemplate oligonucleotide (*12*). (**C**) Labeled DNA duplex was incubated with buffer (lane 1); $E\sigma^{70}$ (lane 2); or $E\sigma^{70}$ preincubated with 6*S* RNA (lane 3); or the M5 control RNA (lane 4). Complexes were challenged with heparin before native gel electrophoresis. (**D**) Labeled nontemplate oligo was examined for binding to $E\sigma^{70}$ as for (C) except without heparin challenge.

plate specificity was confirmed using a mutant 6*S* RNA; M12 contains an A to G mutation at position 43 and directed addition of CTP to ApC but not to ApU (Fig. 2A). Although *E. coli* RNAP can use RNA as a template for RNA synthesis (*16*–*19*), this is the first demonstration of RNAP transcribing a physiologically relevant RNA.

To determine whether 6*S* RNA could direct de novo RNA synthesis, 6*S* RNA:Eσ^{70} complexes were incubated with all four nucleotide triphosphates (NTPs). RNA products (pRNAs) 14 to 20 nucleotides (nt) long were generated when 6*S* and M12 RNAs were used as templates, whereas incubation with the inactive M5 or in the absence of RNA did not produce products (Fig. 2B). Analysis of 5′ end-labeled pRNAs revealed that all these products initiate at the U44 template position (fig. S3). The longest pRNA is 20 nt in length, which indicates that the enzyme terminates before reaching the end of the 6*S* RNA template. We speculate that mechanisms limiting pRNA length may be analogous to those that generate a 20-nt primer at the origin of replication of M13 phage DNA (*20*) and 22- to 30-nt RNA products on single-stranded DNA templates (*21*, *22*). In both cases, the formation of an extended RNA-DNA hybrid [>9 base pairs (bp)] is postulated to result in large-scale RNAP rearrangements, displacement of the 3′ end of the nascent RNA from the active site, and transcription termination (*21*, *22*).

To test whether 6*S* RNA templated RNA-synthesis results in release of 6*S* RNA, 6*S* RNA:Eσ^{70} complexes with labeled 6*S* RNA or with labeled pRNA were examined by native gel electrophoresis (Fig. 3A). After incubation with nucleotides, two new 6*S* RNA–containing complexes with distinct electrophoretic mobilities were detected (compare lanes 2 and 3), and both complexes contained pRNA (lane 6). Migration rates suggested that the more slowly migrating complex contains 6*S* RNA, pRNA, and RNAP, whereas the faster-migrating complex most likely corresponds to 6*S* RNA–pRNA hybrids released from RNAP. To determine which form of RNAP (Eσ^{70} or core) is present in the slower-migrating complex, reactions using His-σ^{70}-RNAP were incubated with Ni-NTA agarose to remove σ^{70}-containing complexes before native gel fractionation. Levels of the 6*S* RNA:Eσ^{70} complex decreased substantially, while levels of other complexes were unchanged (fig. S4), which suggested that σ^{70} is released during the process of RNA synthesis using 6*S* RNA as template.

6*S* RNA–templated synthesis initially appears to follow steps similar to transcription initiation on promoter DNA. However, the transition to longer pRNA synthesis destabilizes 6*S* RNA:RNAP interactions, in sharp contrast to DNA-directed transcription, which leads to the formation of highly stable DNA-pRNA:core complexes. Although σ^{70} is released, the 6*S* RNA–pRNA:core complex is short-lived or destabilized by heparin, as it is not detected after a 2-min heparin challenge (Fig. 3A, lanes 8 and 10). Destabilization may be caused by persistent base-pairing of 6*S* RNA to pRNA as observed when extended RNA:DNA duplexes form on DNA templates lacking nontemplate strands (*23*–*25*). Although 6*S* RNA contains a putative nontemplate strand, it is not able to anneal to the template strand, and we speculate that loss of a reannealing driving force in addition to distinct σ^{70}–6*S* RNA interactions favor formation of an extended RNA:pRNA hybrid over displacement of nascent pRNA.

To determine if and when RNA synthesis from 6*S* RNA occurs in vivo, we first tested whether 6*S* RNA:RNAP complexes could be detected in cell extracts. Two forms of 6*S* RNA with mobility similar to the free 6*S* RNA and 6*S* RNA:Eσ^{70} were detected in extracts from stationary phase cells (Fig. 3B). Incubation of extract with NTPs resulted in formation of a new complex that migrates similarly to 6*S* RNA–

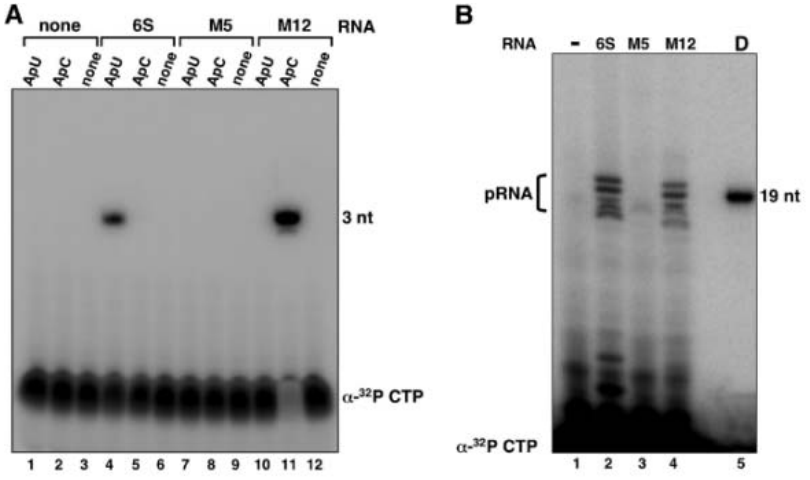

Fig. 2. 6*S* RNA can be used as a template for transcription. (**A**) Eσ^{70} incubated with no RNA or 6*S*, M5, or M12 RNAs was further incubated with ApU, ApC, or no dinucleotide and with [α-^{32}P]CTP. Products were separated on a denaturing polyacrylamide gel. (**B**) As in (A) except transcription was initiated by addition of NTPs and [α-^{32}P]CTP (without dinucleotide). D is an oligonucleotide marker (19 nt).

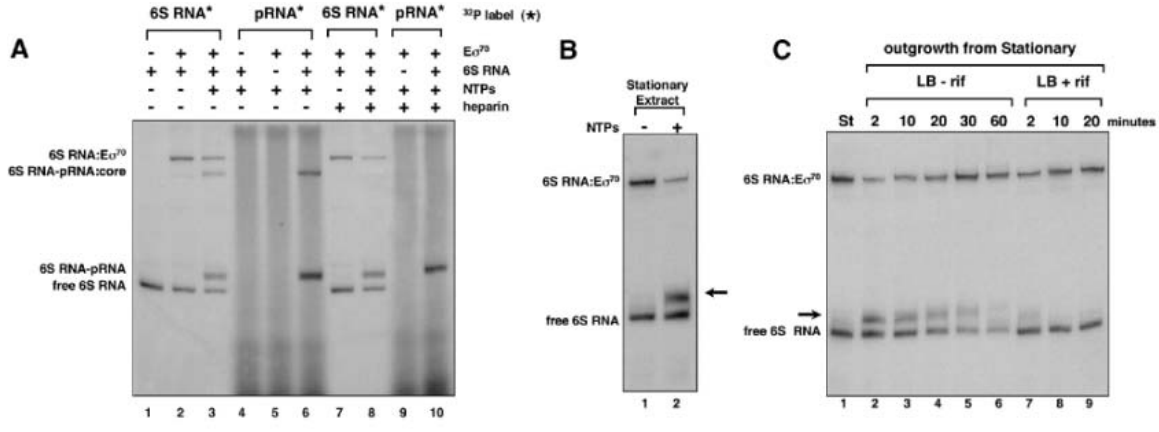

Fig. 3. Transcription from 6*S* RNA occurs in vivo and leads to release of 6*S* RNA from Eσ^{70}. (**A**) Reactions included 6*S* RNA, Eσ^{70} and NTPs as indicated. 6*S* RNA* signifies that [^{32}P]6*S* RNA was used with unlabeled NTPs; pRNA* signifies that [^{32}P]α-CTP was included with NTPs and unlabeled 6*S* RNA. Where indicated, complexes were challenged with heparin before native gel electrophoresis. (**B**) Stationary phase cell extract was incubated in the presence or absence of NTP. (**C**) Extracts from stationary phase cells (St) or cells after growth in LB medium with or without rifampicin (rif) for times indicated. Samples in (B) and (C) were treated with heparin before native gel electrophoresis. For (B) and (C), endogenous 6*S* RNA–containing complexes were detected by Northern analysis using a 6*S* RNA–specific probe.

pRNA, which suggests that 6*S* RNA can be used as a template for transcription in extract. Extract containing samples required heparin treatment to resolve specific complexes on native gels; therefore, 6*S* RNA–pRNA:core complexes were not observed. Gradient fractionation of a stationary phase extract after incubation with NTPs similarly demonstrated significant release of 6*S* RNA from $E\sigma^{70}$ (fig. S5).

The 6*S* RNA:$E\sigma^{70}$ complex is stable in vitro and accumulates to high levels in stationary phase, raising the question of how 6*S* RNA–RNAP interactions are disrupted when cells reinitiate growth. To test if RNA synthesis could mediate timely 6*S* RNA release, endogenous 6*S* RNA complexes were examined in extracts prepared from cells after dilution into rich medium (Fig. 3C). A 6*S* RNA complex with mobility suggesting it was 6*S* RNA–pRNA was detected in extracts from cells 2 to 30 min after dilution. Extracts were not incubated nor NTPs added; therefore, complexes represent those formed in vivo. Addition of an RNAP inhibitor (rifampicin) to the dilution medium prevented 6*S* RNA–pRNA complex formation, which demonstrated that its formation requires RNA synthesis. The presence of 6*S* RNA–pRNA complexes in cells after outgrowth signifies that $E\sigma^{70}$ uses 6*S* RNA as a template for RNA synthesis at this time, consistent with the hypothesis that 6*S* RNA release from $E\sigma^{70}$ could be mediated through this process.

We propose that 6*S* RNA–templated RNA synthesis occurs in response to the rapid increase in NTP pools upon outgrowth (*26*). In vitro RNA synthesis from 6*S* RNA required higher concentrations of NTPs (>50 μM) than several tested DNA promoters (<1 μM NTPs) (fig. S6), which suggests that transcription from 6*S* RNA is more sensitive to NTP concentration. Other factors also may affect the relative stability of 6*S* RNA:$E\sigma^{70}$ complexes or may prevent RNA synthesis from 6*S* RNA, as the 6*S* RNA–pRNA complex was observed only early after exit from stationary phase and did not persist through exponential growth.

In addition to freeing RNAP from 6*S* RNA inhibition, the RNA synthesis reaction likely results in decreased stability of 6*S* RNA. 6*S* RNA levels are decreased during outgrowth (fig. S7) and do not reach maximum levels until well after transition into stationary phase (*7*). Such decreased stability might be due to increased accessibility of 6*S* RNA to cellular nucleases on release from RNAP or could be through direct recognition of the 6*S* RNA–pRNA duplex. It also is tempting to consider whether the pRNA has a cellular function distinct from the role its synthesis has in 6*S* RNA release, especially because the template region within 6*S* RNA is more conserved than the rest of the RNA (*8*).

Control of 6*S* RNA levels and 6*S* RNA–$E\sigma^{70}$ interactions in direct response to NTP concentration create a regulatory circuit where release from RNAP and control of stability of the sRNA inhibitor depend on the same features of the RNA required for its inhibitory nature. Precise positioning of 6*S* RNA in the active site of RNAP blocks DNA promoter binding but allows synthesis-mediated release of 6*S* RNA. The mechanism of 6*S* RNA inhibition appears to differ from FC* and B2 RNA, which do not exclude DNA binding within preinitiation complexes (*4*), which suggests their mechanism of release also will be distinct. However, a common theme for sRNA inhibitors of RNAP may be to exploit inherent properties and activities of the enzyme for its inhibition, as well as for its release from such regulation.

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Supporting Online Material

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Dual Infection with HIV and Malaria Fuels the Spread of Both Diseases in Sub-Saharan Africa

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Mounting evidence has revealed pathological interactions between HIV and malaria in dually infected patients, but the public health implications of the interplay have remained unclear. A transient almost one-log elevation in HIV viral load occurs during febrile malaria episodes; in addition, susceptibility to malaria is enhanced in HIV-infected patients. A mathematical model applied to a setting in Kenya with an adult population of roughly 200,000 estimated that, since 1980, the disease interaction may have been responsible for 8,500 excess HIV infections and 980,000 excess malaria episodes. Co-infection might also have facilitated the geographic expansion of malaria in areas where HIV prevalence is high. Hence, transient and repeated increases in HIV viral load resulting from recurrent co-infection with malaria may be an important factor in promoting the spread of HIV in sub-Saharan Africa.

In Africa, an estimated 40 million people are infected with HIV, resulting in an annual mortality of over 3 million (*1*), whereas over 500 million clinical *Plasmodium falciparum* infections occur every year with more than a million malaria-associated deaths (*2*). There is considerable geographic overlap between the two diseases, particularly in sub-Saharan Africa (*3*), and growing evidence of an interactive pathology (*4–10*). HIV has been shown to increase the risk of malaria infection and the development of clinical malaria, with the greatest impact in immune-suppressed persons (*4*, *6*, *8–10*). Conversely, malaria has been shown to induce HIV-1 replication in vitro (*11*) and in vivo (*5*, *7*). A biological explanation for

these interactions lies in the cellular-based immune responses to HIV and malaria (*11*–*13*).

There is a functional relationship between HIV-1 plasma viral load and transmission probability per coital act, in which a logarithmic increase in viral load is associated with a 2.45-fold increase in transmission probability (*14*). Investigations of HIV-1 transmission probability per stage of infection indicate that the acute stage of HIV infection, during which the viral load peaks at a two-log excess over the chronic stage, plays a pivotal role in transmission (*15*, *16*). This amplification seems to be responsible for as much as half of the infections, at least in the early stages of the epidemic (*16*, *17*). A prospective study of dual infection with HIV and malaria has confirmed and extended earlier findings (*4*–*6*, *8*–*10*) that, first, co-infection leads to a near one-log increase in viral load in chronic-stage HIV-infected patients during febrile malaria episodes (*7*) and, second, HIV infection substantially increases susceptibility to malaria infection (*9*). These findings have highlighted the need for a robust quantitative assessment of the population-level implications of the immune-mediated interaction of the two diseases (*18*).

Thus, we asked the question: does recurrent malaria promote HIV transmission because of a concomitant elevation of viremia during febrile periods? In the absence of field studies that directly measure the effect of malaria on HIV spread, we attempted to answer this question by synthesizing recent quantitative biological findings into a mathematical model that estimates the impact of HIV and malaria on one another (*19*). The core assumptions of our model are shown in Table 1. The duration of the heightened viral load and the impact of co-infection on sexual activity are not adequately characterized parameters. The supporting online material details the bases of our parameter choices and quantifies the impact of the uncertainty in the assumed parameters by means of univariate and multivariate sensitivity analyses (*19*). These analyses indicate a significant role for dual infection in fueling the spread of both diseases in sub-Saharan Africa

We examined the impact of the synergy in Kisumu, Kenya, a setting with high HIV and malaria prevalences. Malaria prevalence refers here to any malaria parasitaemia rather than to clinical disease alone. In the presence of interaction between the two diseases, the HIV epidemic peak is 8% higher whereas the malaria peak is 13% larger than the levels in a scenario where there is no interaction (Fig. 1). The excess prevalence, which is the baseline prevalence subtracted from the prevalence after the inclusion of the interaction, is 2.1% for HIV and 5.1% for malaria, respectively. In the Kisumu district [with an adult human population ≈ 200,000 (*19*)], the interaction in the absence of malaria intervention may account for a cumulative 8,500 excess HIV infections and 980,000 excess malaria episodes since 1980. Furthermore, for the period from 1990 through 2005, a duration marked by an

Table 1. The core assumptions of our HIV/malaria interaction model.

Assumption	Parameter value	Sources
Rate ratio increase in HIV coital transmission probability per one-log (base 10) rise in viral load	2.45	(*14*)
Logarithmic increase in HIV viral load level during malaria infection		
Acute stage	0.0	Assumption
Chronic stage with clinical malaria	0.82	(*7*)
Chronic stage with nonclinical malaria	0.08	(*7*)
Advanced stage	0.20	(*7*)
Susceptibility enhancement to malaria infection in HIV-infected persons		
Acute stage	0%	Assumption
Chronic stage	44%	(*9*, *19*)
Advanced stage	103%	(*9*, *19*)
Duration of heightened viral load during malaria episodes	42 days	(*5*, *7*, *19*)
Fractional reduction in sexual activity during malarial infection		
Clinical malaria	10%	(*19*, *25*, *26*)
Nonclinical malaria	3%	(*7*, *19*)
Fraction of malaria-infected patients developing clinical malaria		
HIV-negative	16%	(*10*)
HIV-positive	31%	(*7*)
Enhanced HIV mortality in dually infected patients		
Areas of stable malaria	0%	(*4*, *10*, *27*)
Areas of nonstable malaria	25%	(*19*, *28*, *29*)

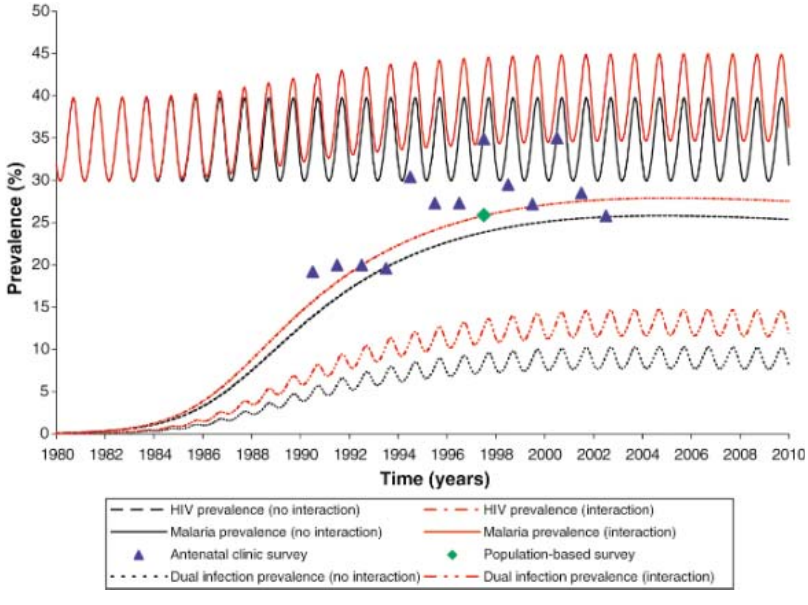

Fig. 1. The time course of HIV and malaria interaction in Kisumu, Kenya. HIV and malaria prevalences in Kisumu as compared with the baseline predictions in the absence of interaction are shown. The measured prevalences were extracted from several studies (*19*).

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average HIV prevalence of roughly 25%, the fraction of HIV infections attributable to malaria is 4.8% whereas that of malaria promoted by HIV is 9.9%. The latter estimate accords well with a derived estimate from rural Uganda (*10*). We estimate that an HIV prevalence that reached 24% in 1995 would have needed two additional years to reach this level in the absence of synergy with malaria.

We proceed to describe the interaction in diverse settings with different HIV and malaria prevalence levels. We characterized the synergy at the endemic equilibrium of both diseases and used the average sexual partner acquisition rate (ρ_{avg}) in the population as a proxy for HIV baseline prevalence level and Macdonald's stability index (MSI) (*20*) as a proxy for that of malaria (*19*). Once we incorporated the interaction between the two diseases in the diverse settings described in Fig. 2, A and B, we derived the excess prevalences (Fig. 2, C and D). It is evident how the interplay, though dependent on baseline measures, can considerably increase HIV and malaria prevalences. The largest increase occurs when one baseline measure is very high while the other is very low and near its endemic threshold. For example, a setting with 1.0% malaria but 37.8% HIV at baseline prevalence transforms into a setting of 9.2% malaria and a barely changed value of 38.5% HIV. When both prevalences are very high, the impact of the interaction is minimal. For HIV, there are two "endemic thresholds" arising for each of the two sexual risk groups assumed in our model. The first threshold is when sexual transmission becomes sustainable in the high-risk group, whereas the other threshold is when the transmission becomes sustainable in the general population (low-risk group) once the partner change rate is high enough to support sustainable transmission, even in the absence of mixing with the high-risk group.

Furthermore, if one of the diseases is at endemic equilibrium while the other is just below its threshold, the interaction can lower the threshold of the second disease, thereby allowing this disease to reach endemic stability. This effect can be seen in Fig. 3, where the interaction has lowered the endemicity threshold for malaria from MSI = 1.353 to 1.270 (a 6% reduction). A myriad of factors, however, affect malaria ecology, so lowering the threshold does not necessarily expand the distribution of malaria. Nevertheless, in areas that can support malaria with a small change in the entomological or transmission parameters, the interaction can drive unstable malaria prevalence toward stability. Though not evident in the figure because of the small absolute change, the interaction has also lowered the HIV endemicity threshold (the threshold of sustainability in the high-risk group) by 6% from $\rho_{avg} = 0.456$ to $\rho_{avg} = 0.430$ partners per year (corresponding to $\rho_{high-risk} = 2.261$ to $\rho_{high-risk} = 2.132$ partners per year).

The rapid increase in excess prevalence in Figs. 2, C and D, and 3 just above the threshold implies that settings with high HIV (or malaria) endemicity but with low or unstable malaria (or HIV) prevalence are particularly at risk for this interaction. Given that, in areas of unstable malaria endemicity, a larger part of the malaria burden is in adults in whom HIV is concentrated, the high HIV prevalence, for example in

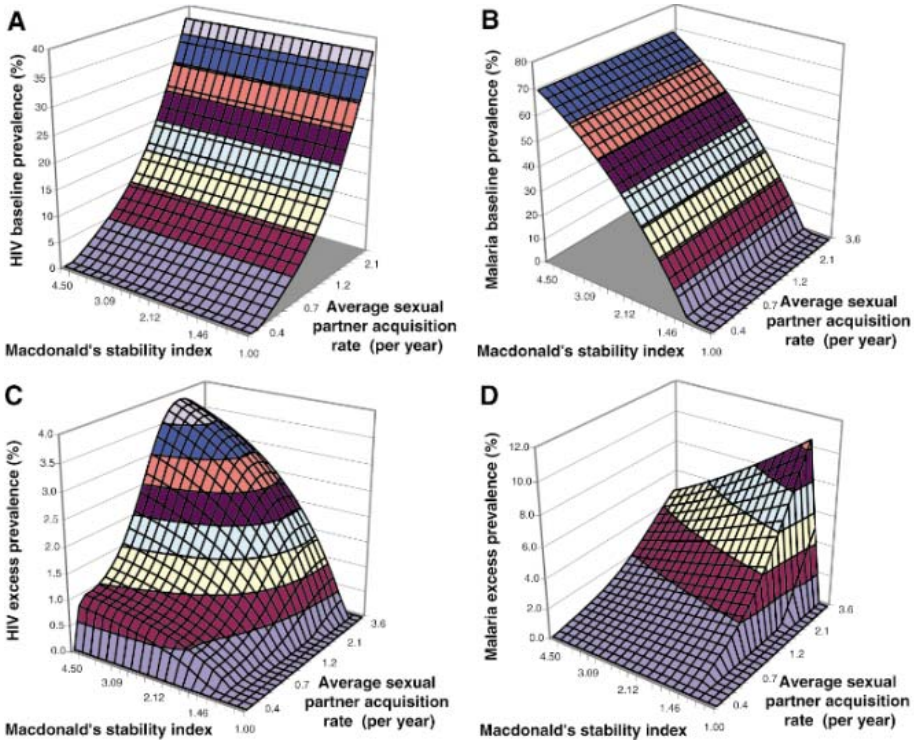

Fig. 2. Excess HIV and malaria prevalences in a wide range of settings. The equilibrium prevalences of HIV (**A**) and malaria (**B**) in the absence of interaction are shown as functions of ρ_{avg} and MSI. Both parameters increase geometrically to capture a wide spectrum corresponding to a change in baseline adult HIV prevalence from 0 to 50% and baseline adult malaria prevalence from 0 to 70%. (**C**) and (**D**) display the corresponding excess HIV and malaria prevalences. Excess prevalence is defined as no-interaction prevalence subtracted from the prevalence in the presence of interaction. Colored gradients correspond to the units in the *Y* axis.

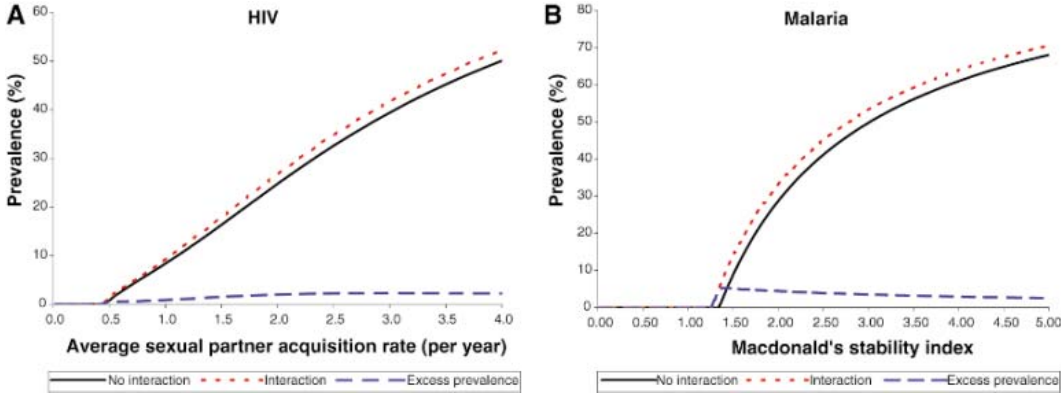

Fig. 3. Interaction impact on shifting endemicity thresholds. (**A**) HIV prevalence in the absence of interaction, in its presence, and in excess prevalence as a function of ρ_{avg} in a setting of 30% malaria baseline prevalence. (**B**) Malaria prevalence in the absence of interaction, in its presence, and in excess prevalence as a function of MSI in a setting of 25% HIV baseline prevalence. Excess prevalence is a manifestation of the shift in the epidemic curves for each of the diseases to below threshold after interaction.

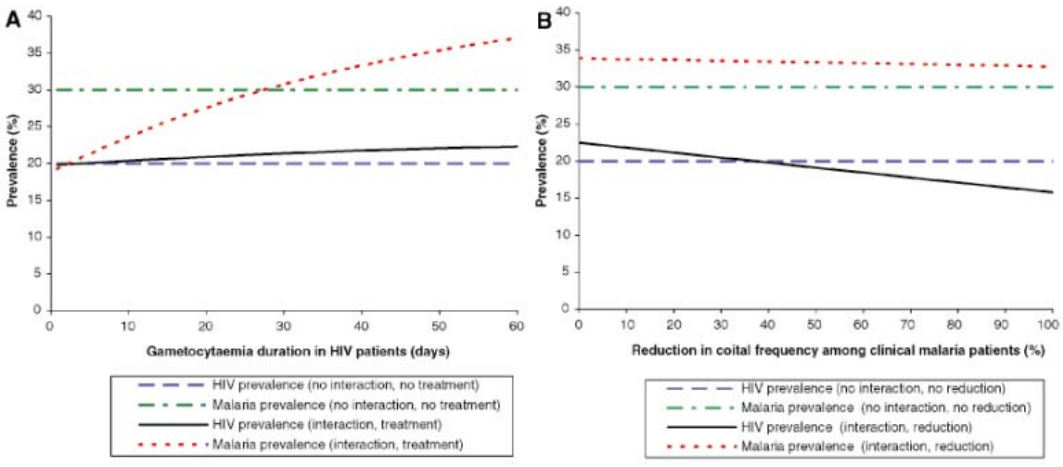

Fig. 4. Impact of potential interventions and the sensitivity of predictions to key assumptions about the parameters of the interaction. (**A**) Impact of malaria treatment on dually infected patients as expressed in HIV and malaria prevalences in the presence of interaction and treatment as compared with the baseline with no interaction and no treatment. The intervention reduces excess prevalence for both diseases, but its impact is stronger on malaria. (**B**) Impact of reducing sexual activity during clinical malaria and HIV dual infection as expressed in HIV and malaria prevalences in the presence of interaction and activity reduction as compared to the baseline with no interaction and no reduction. The intervention reduces excess prevalence for both diseases but its impact is more substantial to the HIV epidemic.

South Africa, can intensify and possibly stabilize malaria endemicity.

Korenromp *et al*. have assessed the impact of HIV on malaria in sub-Saharan Africa and indicated that the overall impact is limited because of differences in geographic distributions and age patterns between the two diseases, although the effect in the presence of geographic overlap can be locally considerable and is substantial in areas of high HIV with unstable malaria as we predict (*21*). In some parts of Africa, the geographic overlap may increase if HIV continues to spread from urban centers to rural areas. Our analysis indicates that the impact on malaria is at its maximum when the number of advanced HIV cases reaches its zenith shortly after the HIV epidemic peaks (Fig. 1), a trajectory akin to that of tuberculosis (*22*). Nonetheless, the malaria peak lags behind that of HIV at most by 1 year, in contrast to that of tuberculosis, which lags by 7 years (*23*).

Our model can be expanded to accommodate general intervention measures such as provision of condoms and insecticide-treated bednets, but here we have focused on measures that target the interaction in co-infected persons. Thus, we have specifically modeled the effect of malaria treatment of HIV-infected patients, assuming either that such treatment shortens the period of heightened HIV viral load or that prophylaxis prevents malaria infection from being established in HIV-infected patients in the first place (*8*). We varied the malaria infectious period (gametocytaemia) from 0 to 60 days in HIV-infected patients (Fig. 4A) and observed a steady decline in excess HIV prevalence as we cut back the duration of malaria episode. However, the outcome showed that malaria treatment is more effective in reducing malaria prevalence than it is at reducing the prevalence of HIV. Shortening gametocytaemia to less than 27 days eliminates all HIV-induced malaria prevalence.

We also tested the impact of a loss of sexual activity during malaria episodes among clinical malaria–infected patients (Fig. 4B). The impact on HIV is considerable, but it is minimal on malaria. A 36% reduction in activity can remove all excess HIV prevalence. Avoidance of sex during, and for 8 weeks after, malarial fever would considerably diminish HIV spread, but this degree of intervention is probably impractical to implement despite key successes in behavioral interventions such as in Uganda (*24*). A more-effective approach may be an emphasis on treatment of malaria and protection against mosquitoes for HIV-infected persons. Thus, linking health services for HIV and malaria would be advantageous. The combination of cotrimoxazole prophylaxis, antiretroviral therapy, and insecticide-impregnated bednets can reduce the incidence of malaria by 95% in HIV-infected persons (*8*).

Our model shows that transient but repeated elevated HIV viral loads associated with recurrent co-infections, such as malaria, can amplify HIV prevalence. This finding suggests one more independent explanatory variable for the high HIV incidence and rapid spread of HIV infection in sub-Saharan Africa. Diseases that are not sexually transmitted can thus affect the natural history of HIV and impact the process of infection spread. Our work highlights the need for field studies that better characterize the parameters of the interaction and explore the impact of intervention measures. However, such studies must account for the ethical considerations posed by the recent findings of Mermin *et al*. (*8*) that there are effective interventions to reduce the incidence of malaria in HIV-infected persons. Finally, we emphasize the need for more-concerted health services for early and effective treatment and prevention of malaria in HIV-infected persons.

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A Positive Feedback Loop Promotes Transcription Surge That Jump-Starts *Salmonella* Virulence Circuit

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The PhoP/PhoQ two-component system is a master regulator of *Salmonella* pathogenicity. Here we report that induction of the PhoP/PhoQ system results in an initial surge of PhoP phosphorylation; the occupancy of target promoters by the PhoP protein; and the transcription of PhoP-activated genes, which then subsides to reach new steady-state levels. This surge in PhoP activity is due to PhoP positively activating its own transcription, because a strain constitutively expressing the PhoP protein attained steady-state levels of activation asymptotically, without the surge. The strain constitutively expressing the PhoP protein was attenuated for virulence in mice, demonstrating that the surge conferred by PhoP's positive feedback loop is necessary to jump-start *Salmonella*'s virulence program.

Unlike obligate parasites, which live in relatively constant environments, free-living organisms need to modulate their gene expression patterns in response to environmental cues. This is conspicuously true for bacterial pathogens, which must express (or silence) distinct sets of genes in the various tissues invaded during infection. This ensures that the encoded products are produced in the correct locales, at the required amounts and for the appropriate extents of time. Consequently, a pathogen's ability to colonize a particular niche and to cause disease is often compromised not only when a virulence regulatory factor is removed but also when it is constitutively activated (*1*, *2*).

The PhoP/PhoQ two-component system is a major regulator of virulence in several Gram-negative species (*3*). Inactivation of the *phoP* or *phoQ* genes renders *Salmonella enterica* serovar Typhimurium five orders of magnitude less virulent for mice and unable to proliferate within phagocytic cells (*4*–*6*). The regulatory protein PhoP governs expression of ~3% of the *Salmonella* genome (*7*) in response to the Mg^{2+} levels sensed by the PhoQ protein: Transcription of PhoP-activated genes is induced in low Mg^{2+} concentrations and repressed in high Mg^{2+} concentrations (*8*), whereas the converse is true for PhoP-repressed determinants. In addition to low Mg^{2+} concentrations, certain antimicrobial peptides have been shown to promote expression of some PhoP-activated genes at intermediate Mg^{2+} concentrations (*9*, *10*).

Previously, the expression of PhoP-regulated genes was examined hours after activation, often by means of stable reporters such as β-galactosidase. To determine the changes in gene transcription taking place immediately after activation of the PhoP/PhoQ system, we investigated the expression kinetics of PhoP-regulated genes by isolating RNA as early as 5 min after *Salmonella* were shifted from media containing repressing (10 mM) to activating (50 μM) Mg^{2+} concentrations. The mRNA levels of the PhoP-activated *mgtA*, *phoP*, *pmrD*, and *mig-14* genes increased after the shift to low Mg^{2+}concentration, reached a peak, and then decreased to attain steady-state levels that were 20 to 50% of the maximum (Fig. 1, A to D). A similar kinetic behavior was observed when *Salmonella* were induced in media with 200 μM Mg^{2+}, which activates the PhoP/PhoQ system less than does 50 μM Mg^{2+} (*8*): The mRNA levels of the PhoP-activated genes increased, reached a peak that was lower than that obtained when *Salmonella* was induced at 50 μM Mg^{2+} (except for the *mgtA* gene, which reached the same levels), and then decreased (Fig. 1, A to D). These results demonstrated that activation of the PhoP/PhoQ system promotes a surge in the mRNA levels of PhoP-regulated genes, and that this surge is not specific to a particular PhoP-activated gene or inducing condition (*11*).

To examine whether the observed changes in mRNA levels were due to binding of the PhoP protein to its target promoters, we carried out chromatin immunoprecipitation (ChIP) experiments in organisms that were shifted from media with repressing (10 mM) to inducing (50 μM) Mg^{2+} concentrations. Occupancy of the *mgtA* and *pmrD* promoters by the PhoP protein, which was detected immediately after the shift, peaked at 20 min and then decreased to reach new steady-state levels (Fig. 2A) (*12*).

The decrease in promoter occupancy and gene transcription taking place 20 min after induction of the PhoP/PhoQ system could reflect degradation of the PhoP protein and/or a reduction of its activity. We could rule out the first possibility because the PhoP protein levels increased for at least 60 min (Fig. 2B), which is in agreement with the PhoP/PhoQ system autogenously activating its own expression (Fig. 1B) (*13*). We have previously demonstrated that phosphorylated PhoP is the form of the PhoP protein that binds to its target promoters and activates gene transcription in vivo (*14*). Thus, we investigated the levels of phosphorylated PhoP protein in organisms that were grown under repressing (10 mM) Mg^{2+} concentrations and were then shifted to media with inducing (50 μM) Mg^{2+} concentrations and pulsed with $^{32}PO_4$. Immunoprecipitation of the PhoP protein revealed that the levels of phospho-PhoP increased after the shift to low-Mg^{2+} media, peaking at 15 min; were decreasing by 30 min; and stabilized at 20% of the maximum levels by 60 min (Fig. 2C). This is in spite of the fact that the total amount of PhoP protein increased during this time frame (Fig. 2B). Together, these data suggest that the changes in promoter occupancy by the PhoP protein and in mRNA amounts of PhoP-activated genes reflect the levels of phospho-PhoP protein.

The PhoP and PhoQ proteins are encoded in a bi-cistronic operon that is transcribed from two promoters: a constitutive promoter that provides the basal levels of these proteins required for sensing and responding to changes in environmental conditions, and a regulated promoter that is activated by the PhoP protein

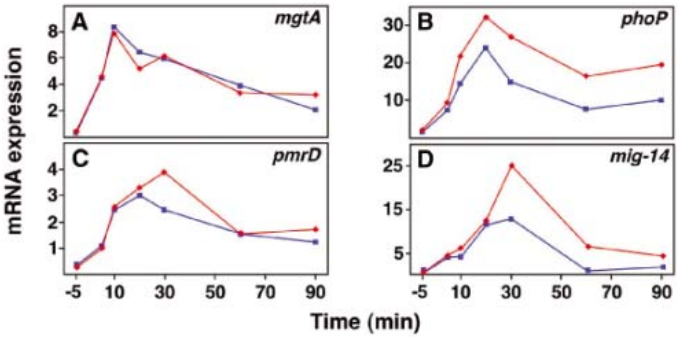

Fig. 1. Induction of the PhoP/PhoQ system by the low-Mg^{2+} signal results in a surge in PhoP-regulated gene transcription. (**A** to **D**) The mRNA levels of the *mgtA*, *phoP*, *pmrD*, and *mig-14* genes determined by real-time polymerase chain reaction (PCR) analysis using RNA prepared from wild-type (EG13918) (*10*) cells that were grown in medium containing 10 mM Mg^{2+}, shifted to medium with either 50 μM (red lines) or 200 μM (blue lines) Mg^{2+}, and harvested at the designated times. Expression levels were normalized to those of the 16*S* ribosomal RNA gene.

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when the bacterium experiences the low-Mg^{2+} inducing signal (*8*, *13*). To test the possibility that positive autoregulation of the *phoPQ* operon is involved in the peak of activity of the phospho-PhoP protein, we compared the kinetics of promoter occupancy and gene transcription in two isogenic strains: one with the wild-type *phoPQ* promoter [that is, harboring the PhoP box that is responsible for transcriptional autoregulation (*13*)] and one in which the PhoP box was replaced by a consensus –35 sequence (Fig. 3A). Western blot analysis of extracts prepared from the strain with the wild-type *phoPQ* promoter revealed that the PhoP protein was detected only in organisms induced in low Mg^{2+} concentrations, which promoted a continuous increase in the PhoP protein levels during the first 45 min (Fig. 3B). In contrast, the strain with the –35 sequence in the *phoPQ* promoter produced the PhoP protein constitutively (Fig. 3B) at levels that were similar to the steady-state levels achieved by the strain with the wild-type *phoPQ* promoter after induction of the PhoP/PhoQ system (Fig. 3B). This allowed us to compare promoter occupancy and PhoP-mediated transcription in strains that differed only in the time required to produce steady-state levels of the PhoP protein. Despite synthesizing the PhoP protein constitutively, there was no occupancy of PhoP-activated promoters (Fig. 3C) or transcription of PhoP-activated genes (Fig. 3D) in the strain with the –35 sequence in the *phoPQ* promoter growing under repressing conditions.

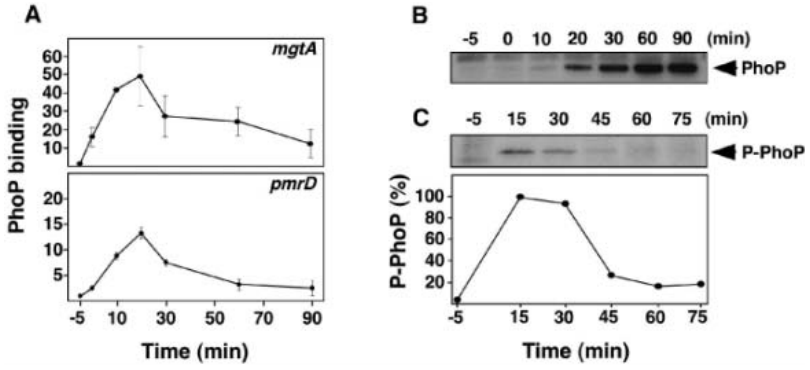

Fig. 2. The surge in promoter occupancy by the PhoP protein is due to changes in the levels of phosphorylated PhoP protein. (**A**) Promoter occupancy by the PhoP protein determined by ChIP assay using wild-type (EG13918) cells that were grown in repressing (10 mM) Mg^{2+} concentrations, shifted to activating (50 μM) Mg^{2+} concentrations, and harvested after the addition of formaldehyde at the indicated times. Occupancy was quantified using real-time PCR analysis. The values of PhoP binding were obtained from normalization of PhoP occupancy (ratio of DNA bound by the PhoP protein to DNA not bound by the PhoP protein) of the target promoter to that of the endogenous control *rpoD* promoter. Error bars show the standard deviation from the mean. The levels of total (**B**) and phosphorylated (**C**) PhoP protein were determined using extracts from EG13918 cells that were grown in medium containing a high (10 mM) Mg^{2+} concentration, shifted to medium with low (50 μM) Mg^{2+} concentration, and harvested at the designated times. The levels of phospho-PhoP (P-PhoP) were quantified by phosphoimager analysis and normalized to the maximal level. The extracts were prepared from aliquots of cells normalized by optical density at 600 mm. and used for both Western blot and immunoprecipitation experiments.

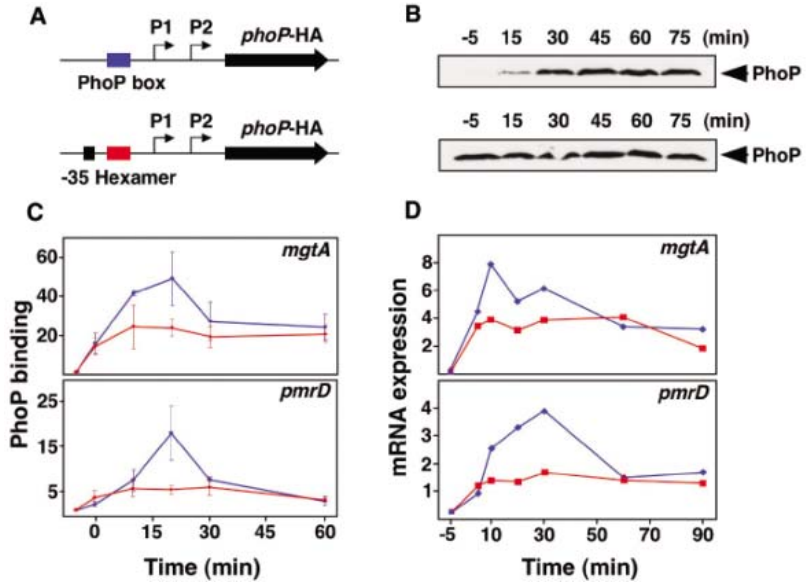

Fig. 3. The positive feedback loop of the *phoPQ* operon is necessary for the surge in activity of the PhoP/PhoQ system. (**A**) Schematic representation of the *phoPQ* promoter in isogenic strains EG13918 (top) and EG14943 (bottom). Strain EG13918 harbors the wild-type P1 promoter, which is positively autoregulated by the PhoP protein and the constitutive P2 promoter (*8*, *13*). Strain EG14943 harbors a consensus –35 hexameric sequence (red square) in place of the PhoP box (blue square). The black square indicates the "scar" sequence generated during the construction of the strains (*34*). (**B**) The levels of total PhoP protein were determined using extracts prepared from equivalent numbers of EG13918 (top) and EG14943 (bottom) cells after switching Mg^{2+} concentrations as described in Fig. 2. The levels of promoter occupancy by the PhoP protein (**C**) and mRNA expression (**D**) of the *mgtA* and *pmrD* genes were determined in strains EG13918 (blue) and EG14943 (red) that were shifted from media with 10 mM to 50 μM Mg^{2+} concentrations. The values for PhoP binding and mRNA expression were obtained as described in the legends of Figs. 1 and 2.

When the strain expressing the PhoP protein constitutively was shifted from repressing (10 mM) to inducing (50 μM) Mg^{2+} concentrations, binding of PhoP to the *mgtA* and *pmrD* promoters (Fig. 3C) and transcription of the respective genes (Fig. 3D) increased during the first 10 min and then asymptotically reached the steady-state levels displayed by the strain with the wild-type *phoPQ* promoter (*15*). In agreement with these results, the levels of phospho-PhoP increased upon the shift from high to low Mg^{2+} concentration and reached constant levels that were only ~20% of the peak levels exhibited by the strain with the wild-type *phoPQ* promoter. Thus, positive autoregulation of the PhoP/PhoQ system is necessary for the surge in activity triggered by the low-Mg^{2+} inducing signal.

To determine whether the autoregulation-dependent surge in PhoP activity has a role in virulence, mice were inoculated with the two isogenic strains differing in the *phoPQ* promoter. All the mice inoculated with *Salmonella* bearing the wild-type *phoPQ* promoter died. In contrast, all the mice inoculated with the strain harboring the mutant *phoPQ* promoter with the –35 sequence replacing the PhoP box and expressing the PhoP protein constitutively survived (Fig. 4) (*16*). These results demonstrate that the surge in phospho-PhoP activity conferred by the PhoP/PhoQ positive feedback loop is essential for *Salmonella* virulence. Moreover, they imply that *Salmonella*'s ability to cause a lethal infection in mice requires the rapid expression of PhoP-activated gene products and/or rapid repression of PhoP-repressed gene

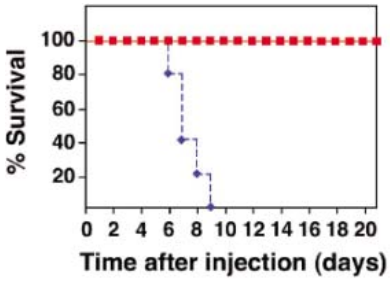

Fig. 4. Positive autoregulation of the *phoPQ* operon is required for *Salmonella* virulence in mice. C3H/HeN mice were injected intraperitoneally with ~10^3 cells of wild-type *Salmonella* (EG13918, blue) and its isogenic mutant constitutively expressing the PhoP protein (EG14943 strain, red). None of the mice infected with EG14943 strain died during the first 3 weeks, whereas all the mice infected with strain EG13918 with the wild-type *phoPQ* promoter died. The survival assay was performed twice independently with groups of five mice per strain. Shown is the result of one of the two experiments, which gave similar results. The survival kinetics of mice infected with wild-type *Salmonella* strain 14028s was similar to that of mice infected with strain EG13918 (not shown in the figure).

products. These might include virulence regulatory proteins such as the two-component system SpiR/SsrB (*17*), the transcriptional activators SlyA (*18*) and HilA (*19*), the alternative sigma factor RpoS (*20*), and/or virulence structural proteins such as MgtC (*21*), Mig-14 (*22*), and NagA (*23*).

The PhoQ protein can modify the levels of phospho-PhoP in vitro (*24*, *25*), suggesting that it was probably responsible for the changes in the levels of phospho-PhoP observed in vivo (Fig. 2C). Thus, we compared the behavior of two isogenic strains expressing either a wild-type PhoQ protein or one with a single amino acid substitution that compromises its phosphatase activity (*14*). We used strains in which the chromosomal copy of the *phoPQ* operon had been deleted and that harbored a plasmid with the *phoP-HA* and *phoQ* genes under the control of a derivative of the *lac* promoter (*14*) because a strain with a chromosomal *phoQ* mutation encoding a phosphatase-defective PhoQ would constitutively activate the PhoP protein. We were able to identify a condition (0.5 mM isopropyl-β-D-thiogalactopyranoside and 33 μM Mg^{2+}) for the strain expressing the wild-type PhoQ protein that promoted a transcription pattern (fig. S3A) mimicking that displayed by the autoregulated strain induced in low-Mg^{2+} media (Fig. 1), reflecting the levels of phospho-PhoP protein in the cell (fig. S3B). In contrast, the mRNA levels of PhoP-activated genes did not decrease after the initial increase in the isogenic strain expressing the mutant PhoQ protein (fig. S3A), which is consistent with the persistently high levels of phospho-PhoP protein (fig. S3C). These results demonstrate that the PhoQ protein governs the levels of phospho-PhoP protein in vivo. Furthermore, they suggest that there is a temporal change in the kinase and phosphatase activities of PhoQ after activation of the PhoP/PhoQ system.

The activation surge displayed by PhoP/PhoQ is exhibited by other two-component systems. For example, activation of the PmrA/PmrB system (*26*, *27*) by growing *Salmonella* in media containing a high (10 mM) Mg^{2+} concentration and then shifting it to media containing a low (50 μM) Mg^{2+} concentration and 100 μM Fe^{3+} resulted in an increase in the mRNA levels corresponding to the PmrA-activated *pbgP* and *pmrC* genes, which peaked and then reached new steady-state levels (fig. S4A), reflecting changes in the amount of phospho-PmrA protein (fig. S4B). These data indicate that, like the PhoP/PhoQ system, the positively autoregulated PmrA/PmrB system (*28*, *29*) responds to its specific signal by promoting an initial activation followed by lower steady-state levels.

A transient increase in the mRNA levels of the targets of regulation of the copper-responding CusR/CusS system from *Escherichia coli* (*30*), the vancomycin-responding VanR/VanS system from *Streptomyces coelicolor* (*31*), and the peptide pheromone–responding ComE/ComD system from *Streptococcus pneumoniae* (*32*) has also been observed when these two-component systems were activated by their respective signals. Additionally, constitutive expression of the *comDE* genes inhibited the development of competence in *S. pneumoniae* (*33*). Cumulatively, these findings indicate that the activation surge described for PhoP/PhoQ (Figs. 1 and 2) and PmrA/PmrB (fig. S4) is not exclusive to virulence-related systems from *Salmonella* and may be exhibited by systems having different physiological functions in diverse bacterial species. The one correlating factor is that all these systems positively autoregulate their own expression, which in the case of the *Salmonella* PhoP/PhoQ system is required for the normal surge of activity (Fig. 2) and virulence (Fig. 4) in mice.

What is the significance of response curves (Figs. 1 and 2 and fig. S4) in which regulatory systems display a peak of activity before reaching new steady-state levels? The initial activation may allow the immediate establishment of a new phenotypic state. This would enable an organism to carry out the necessary tasks required to face the condition that triggered activation of the regulatory system. The steady-state levels of expression that follow the initial activation would then serve to maintain the new phenotypic state.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5805/1607/DC1
Materials and Methods
Figs. S1 to S5
Tables S1 to S3
References

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Sequential Interplay of Nicotinic and GABAergic Signaling Guides Neuronal Development

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GABA (γ-aminobutyric acid), the major inhibitory transmitter in the brain, goes through a transitory phase of excitation during development. The excitatory phase promotes neuronal growth and integration into circuits. We show here that spontaneous nicotinic cholinergic activity is responsible for terminating GABAergic excitation and initiating inhibition. It does so by changing chloride transporter levels, shifting the driving force on GABA-induced currents. The timing of the transition is critical, because the two phases of GABAergic signaling provide contrasting developmental instructions. Synergistic with nicotinic excitation, GABAergic inhibition constrains neuronal morphology and innervation. The results reveal a multitiered activity-dependent strategy controlling neuronal development.

GABA (γ-aminobutyric acid) is the main inhibitory neurotransmitter in the adult brain, but GABAergic transmission is excitatory during early stages of development because of a reversed chloride gradient (*1*–*3*). The GABAergic excitatory period is critical for neuronal maturation and integration into circuits during embryonic development and after adult neurogenesis (*2*, *4*–*6*). Despite the profound impact of the GABAergic excitation/inhibition transition on the nervous system, little is known about mechanisms that determine the timing of the transition or about possible developmental consequences of subsequent inhibitory GABAergic input. We show here that endogenous nicotinic cholinergic activity drives maturation of GABAergic signaling, determining when it becomes inhibitory. Further, early GABAergic inhibition interacts synergistically with nicotinic cholinergic signaling to guide subsequent development in new directions. These are unexpected consequences of spontaneous nicotinic activity.

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Pharmacological blockade of nicotinic acetylcholine receptors (nAChRs) in vivo revealed the effects of spontaneous nicotinic cholinergic activity on GABAergic maturation. An informative example is the chick ciliary ganglion (CG), which receives nicotinic synaptic input from the accessory oculomotor nucleus and innervates smooth and striated muscle in the eye (*7*). In addition to nAChRs, CG neurons express $GABA_A$ receptors (*8*) and, we find, receive GABAergic input (fig. S1). GABAergic excitation in developing neurons can be visualized by loading cells with the calcium fluor fluo-3AM and challenging with GABA (*9*). The resulting depolarization triggers calcium influx through voltage-gated calcium channels (VGCCs), causing fluorescence. GABA induced fluorescent responses in freshly dissociated embryonic day 9 (E9) CG neurons loaded with fluo-3AM (Fig. 1, A to C). Fewer neurons from older ganglia displayed GABA-induced fluorescence; by E14 the response was almost gone. The decrease was not due to loss of VGCCs (Fig. 1, A and B) or $GABA_A$ receptors but rather to a loss of depolarizing GABA responses. Unexpectedly, this developmental change was prevented by the application of nicotinic antagonists in ovo. Blockade of nAChRs containing α7 subunits (α7-nAChRs) with either 100 nM α-bungarotoxin (αBgt) or 20 nM methyllycaconitine (MLA) at E8 caused more than a third of E14 neurons to retain a GABA-induced calcium response (Fig. 1D). Blocking the other major nicotinic receptor expressed by the neurons [i.e., heteromeric

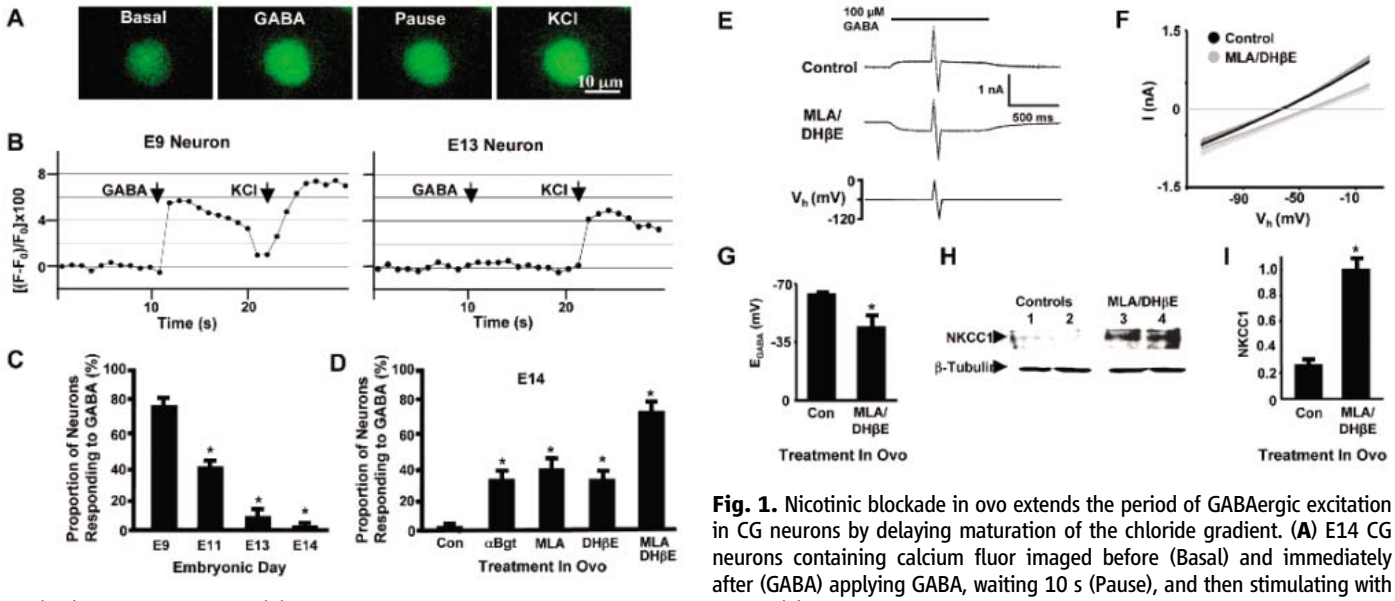

Fig. 1. Nicotinic blockade in ovo extends the period of GABAergic excitation in CG neurons by delaying maturation of the chloride gradient. (**A**) E14 CG neurons containing calcium fluor imaged before (Basal) and immediately after (GABA) applying GABA, waiting 10 s (Pause), and then stimulating with KCl (KCl). Scale bar, 10 μm. (**B**) Fluorescence responses of an E9 and an E13 neuron. (**C**) GABA-induced calcium fluorescence is largely lost in CG neurons between E9 and E14. (**D**) In ovo application of nicotinic antagonists at E8 caused the neurons to retain a GABA-induced calcium fluorescence response at E14. Con, sham-operated control. Values represent the mean ± SEM (n = 18 cultures from six experiments; 200 to 350 neurons per condition). *, $P \leq 0.001$ versus E9 for (C), and versus Con for (D) by analysis of variance (ANOVA). (**E**) Perforated patch-clamp recordings from E14 neurons from a control (top) and MLA/DHβE-treated (middle) embryo in response to applied voltage (V_h; bottom). (**F**) Mean GABA-induced current as a function of V_h in neurons from control (dark line) and MLA/DHβE-treated (light line) embryos. Line widths indicate SEM (n = 7). (**G**) Mean interpolated GABA reversal potential for neurons from control and MLA/DHβE-treated embryos. *, $P < 0.05$, unpaired Student's t test. (**H**) Western blots of E14 CGs from control and MLA/DHβE-treated embryos, probed with antibodies to NKCC1 and β-tubulin (type III). (**I**) Quantification of NKCC1 on Western blots (n = 6 lanes/condition; 10 CGs per lane).

α3-containing receptors (α3*-nAChRs)] with 5 μM dihydro-β-erythroidine (DHβE) had a similar effect. Combining blockers for the two receptor types completely prevented loss of the GABA-induced fluorescence response (Fig. 1D). No morphological differences or changes in body weight were apparent for MLA/DHβE-treated embryos versus vehicle-treated controls.

The loss of GABA-induced calcium fluorescence resulted from maturation of the chloride gradient. Patch-clamp recording from E14 neurons in voltage-clamp mode using the perforated patch technique to preserve the endogenous chloride gradient revealed GABA responses with highly negative reversal potentials (–63.7 ± 1.3 mV; mean ± SEM, $n = 7$) (Fig. 1, E to G). In contrast, E14 neurons from embryos blocked with MLA and DHβE at E8 in ovo had a more depolarized reversal potential for the GABA response (–44.1 ± 7.2 mV) (Fig. 1, E to G), as expected for immature neurons. Western blot analysis of E14 CGs from controls and MLA/DHβE-treated embryos showed that nicotinic blockade enabled ganglia to retain much higher levels of the embryonic chloride transporter NKCC1 (Fig. 1, H and I), which produces the depolarizing chloride gradients found early in development (*1*, *3*). We conclude that blockade of nicotinic transmission between E8 and E14 prevents maturation of the chloride gradient in part by maintaining high levels of NKCC1.

To evaluate the pervasiveness of nicotinic effects on GABAergic maturation, we examined central nervous system populations. Freshly dissociated chick spinal cord neurons loaded with fluo-3AM were challenged with GABA plus glycine, the predominant inhibitory transmitters in the adult spinal cord. Whereas more than 75% of E6 neurons had GABA/glycine–induced calcium responses, less than 10% did so at E9 (fig. S2). Treating the embryos with MLA/DHβE from E3 in ovo caused nearly half of the neurons to retain GABA/glycine–induced calcium rsponses at E9. Hence, endogenous nicotinic activity helps drive conversion of GABAergic excitation to inhibition in spinal cord neurons.

In rodent hippocampal neurons, the GABAergic conversion occurs during the first weeks of postnatal life, a time when α7-nAChRs reach peak levels in the tissue (*10*, *11*). The α7-nAChR has a high relative calcium permeability (*12*), and calcium influx promotes GABAergic conversion by increasing expression of the chloride transporter KCC2 that decreases intracellular chloride (*13*). Accordingly, we compared hippocampal neurons from wild-type and mutant mice lacking a functional α7-nAChR gene (*14*). Freshly dissociated wild-type neurons displayed GABA-induced calcium elevations at postnatal day 6 (P6), whereas less than 20% did so at P13 (Fig. 2A). Hippocampal neurons from α7-nAChR knockout (KO) mice showed a very different profile. Most retained the excitatory GABA response at P9, and more than 50% still displayed it at P13 (Fig. 2A).

A depolarizing chloride gradient resulting from an immature expression pattern of chloride transporters in hippocampal cells again appeared to be responsible for the extended period of GABAergic excitation. Western blot analysis indicated that hippocampal tissue from α7 KO mice had higher levels of NKCC1 (Fig. 2B) and lower levels of KCC2 (Fig. 2C) than did age-matched wild-type tissue. The results suggest that deletion of α7-nAChRs causes the cells to retain an immature expression pattern of chloride transporters (high NKCC1, low KCC2) (*1*, *3*, *11*).

GABAergic inhibition, we find, plays an active role during development, enabling nicotinic excitation to guide neuronal development in a different direction. E8 chick CG neurons readily form nicotinic synapses in culture (*15*) but remain immature for at least 6 days, as evidenced by their retention of a depolarizing GABA response that supports calcium fluorescence (fig. S3). Forcing expression of KCC2 by transfecting a construct encoding KCC2 fused to green fluorescent protein (KCC2/GFP) eliminated the GABA-induced calcium fluorescence as expected (fig. S3). Striking morphological differences were found for KCC2/GFP-expressing neurons after chronic exposure to GABA. They became unipolar in culture as found in vivo. If GABA was omitted or if GFP was expressed in the neurons instead of KCC2/GFP, the neurons remained multipolar (Fig. 3A-C). Notably, the GABA-induced morphological change required nicotinic activity: Including MLA and DHβE in the medium to block α7- and α3*-nAChRs, respectively, for the 6-day period prevented the change (Fig. 3D). Neurons treated with the nicotinic blockers alone remained multipolar (not different from GFP).

A similar pattern emerged when synaptic contacts positioned on the neurons were examined. Staining for SV2 as a presynaptic marker revealed puncta on E8 neurons grown in culture for 6 days. Chronically treating KCC2/GFP-expressing neurons with GABA reduced the number of SV2 puncta compared with those found on untransfected neighboring cells (Fig. 3, E and F). No reduction was seen for neurons expressing GFP or for KCC2/GFP-expressing neurons treated with the $GABA_A$ receptor antagonist gabazine instead of GABA (Fig. 3F). Adding MLA and DHβE to the culture medium prevented the GABA-induced reduction of SV2 puncta on KCC2/GFP-expressing neurons but had no effect on the levels seen when gabazine was substituted for GABA (Fig. 3F). The results show that again GABAergic inhibition and nicotinic excitation must combine to produce the changes.

How might this occur? Nicotinic activity can regulate gene expression in chick CG neurons but only if VGCCs fail to activate (*16*). Inhibitory GABAergic signaling could prevent nicotinic transmission from activating VGCCs. Evidence for this was obtained by examining the ability of nicotine to induce sustained activation of the transcription factor CREB [cyclic adenosine monophosphate (cAMP) response element–binding protein] under conditions previously shown to correlate with nicotine-induced changes in gene expression (*16*). VGCC blockers such as cadmium enable nicotine to activate CREB in freshly dissociated E14 neurons. GABA substituted for cadmium in this respect, acting through $GABA_A$ receptors; gabazine prevented the GABA effect (fig. S4A). GABA was unable to support nicotine-induced CREB activation in neurons that had depolarizing GABA responses (fig. S4B). Thus, E14 neurons from embryos treated with MLA and DHβE at E8 in ovo did not show activated CREB when treated with nicotine plus GABA but could still

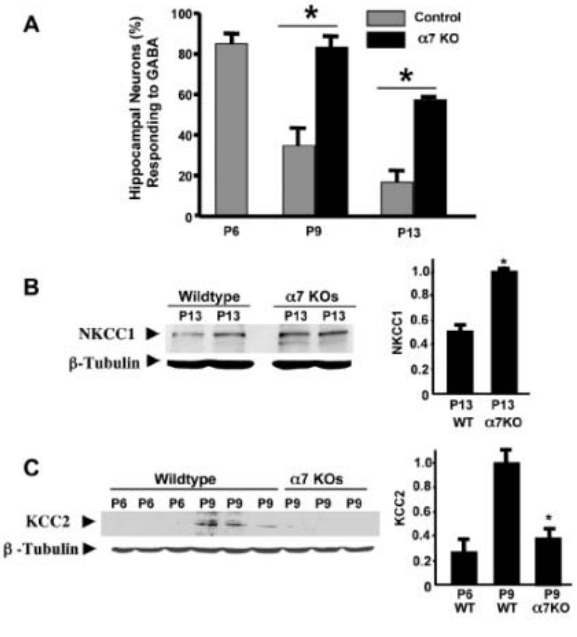

Fig. 2. Inactivating the α7-nAChR gene extends the developmental period in which GABA depolarizes neurons and prolongs an immature pattern of chloride transporters in the hippocampus. (**A**) Hippocampal neurons dissociated from P6, P9, and P13 wild-type (control) or α7-nAChR KO (α7 KO) mice were imaged for GABA- and KCl-induced calcium fluorescence as in Fig. 1 (mean ± SEM for 12 cultures from four experiments; 400 to 500 neurons per condition). *, $P \leq 0.01$. (**B**) Western blots of P13 control and α7 KO hippocampi probed for NKCC1 and β-tubulin (left); quantification (right), mean ± SEM ($n = 6$ mice per condition from three experiments). (**C**) Western blots of P6 and P9 control and α7 KO hippocampi showing KCC2 and β-tubulin (left); quantification (right) as in B. *, $P \leq 0.001$ compared with age-matched wild-type in (B) and (C).

do so in response to nicotine plus cadmium (fig. S4B). The results are consistent with GABAergic inhibition sufficiently suppressing VGCC activation to permit nicotinic alteration of gene expression (fig. S5) (*16*).

To determine whether GABAergic inhibition and nicotinic excitation also act synergistically to guide development in vivo, we electroporated the KCC2/GFP construct into chick CG precursors at E1.5 in ovo (*17*). Imaging CG sections at E14 revealed neurons expressing the construct. The small, round choroid cells that make up half of the neurons in the ganglion expressed normal numbers of α7-nAChR clusters but received few presynaptic boutons marked by SV2 staining (Fig. 4, A to D). Choroid neurons transfected with the GFP construct, in contrast, had normal levels of SV2 puncta on the soma (Fig. 4, E to H). Early expression of KCC2, together with GABAergic input, apparently depressed innervation of choroid neurons. The critical experiment then involved replicating the KCC2/GFP electroporation at E1.5, applying the nicotinic blockers MLA and DHβE to the embryo at E3, and isolating the cells at E14 for testing. The nicotinic blockers prevented the reduction in SV2 puncta (Fig. 4, I to L). Quantifying either the total amount of SV2 staining associated with boutons (Fig. 4M) or the number of SV2-stained boutons (Fig. 4N) yielded the same conclusions.

The results show that endogenous nicotinic activity acts broadly throughout the nervous system to convert GABAergic signaling from excitation to inhibition in developing neurons. The mechanism is likely to involve a change in chloride transporter levels, making the equilibrium potential for chloride currents more negative. In some cases, the GABAergic conversion may be mediated directly by activation of α7-nAChRs on the cells, given the presence of the receptors at the relevant time, their ability to be activated both by choline and acetylcholine, and their high relative permeability to calcium (*10*, *12*, *18*, *19*). In other cases, the effect may be indirect, acting perhaps through excitatory GABAergic projections. In the hippocampus, α7-nAChRs are most prominent on interneurons (*20*), and GABAergic excitatory input can facilitate GABAergic conversion (*13*). Repetitive spontaneous waves of excitation, driven initially by nicotinic activity and dependent on GABA/glycine, spread throughout the retina and spinal cord during development and influence the pattern of connections formed (*21*–*24*). The developing hippocampus also has spontaneous waves dependent on GABAergic excitation and subject to nicotinic modulation (*25*, *26*).

Previous work showed that GABAergic excitation is important for early neuronal development and integration into circuits (*2*, *4*–*6*). Our findings indicate that GABAergic inhibition, in concert with nicotinic excitation, is important for later stages of development. In the CG this is likely to result from GABA suppressing VGCC activation during nicotinic excitation, a condition that enables nicotinic input to alter gene expression in the ganglion (*16*). Because calcium influx is a common mechanism by which excitation influences neuronal development and because the amount and distribution of calcium influx is critical for the outcome (*27*, *28*), the ability of GABAergic in-

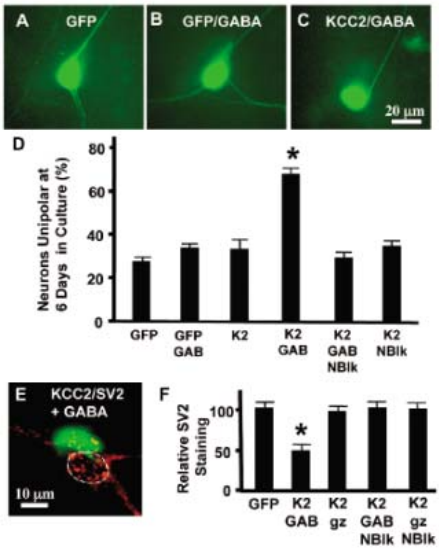

Fig. 3. GABA induces developmental changes in neurite number and synaptic contacts when neurons in culture express KCC2. E8 CG neurons transfected with GFP or KCC2-GFP constructs were imaged after 6 days before (A to D) or after (E and F) permeabilizing and immunostaining for SV2. (**A**) GFP, multipolar. (**B**) GFP/GABA, multipolar. (**C**) KCC2/GABA, unipolar. (**D**) Quantification showing increased proportion of unipolar neurons when expressing KCC2 (K2) and treated with GABA (GAB) unless nicotinic blockers (MLA/DHβE) are present in culture (NBlk). (**E**) SV2 staining (red) on KCC2-transfected neuron (green) and adjacent control neuron (dashed line). (**F**) Quantification showing SV2 staining levels relative to adjacent untransfected neuron. Values represent mean ± SEM (n = 12 to 16 cultures per condition from six to eight experiments; 60 to 300 neurons per condition). Scale bars, 20 μm in (A) to (C), 10 μm in (E). *, P < 0.001 in (D), P < 0.01 in (F), by ANOVA.

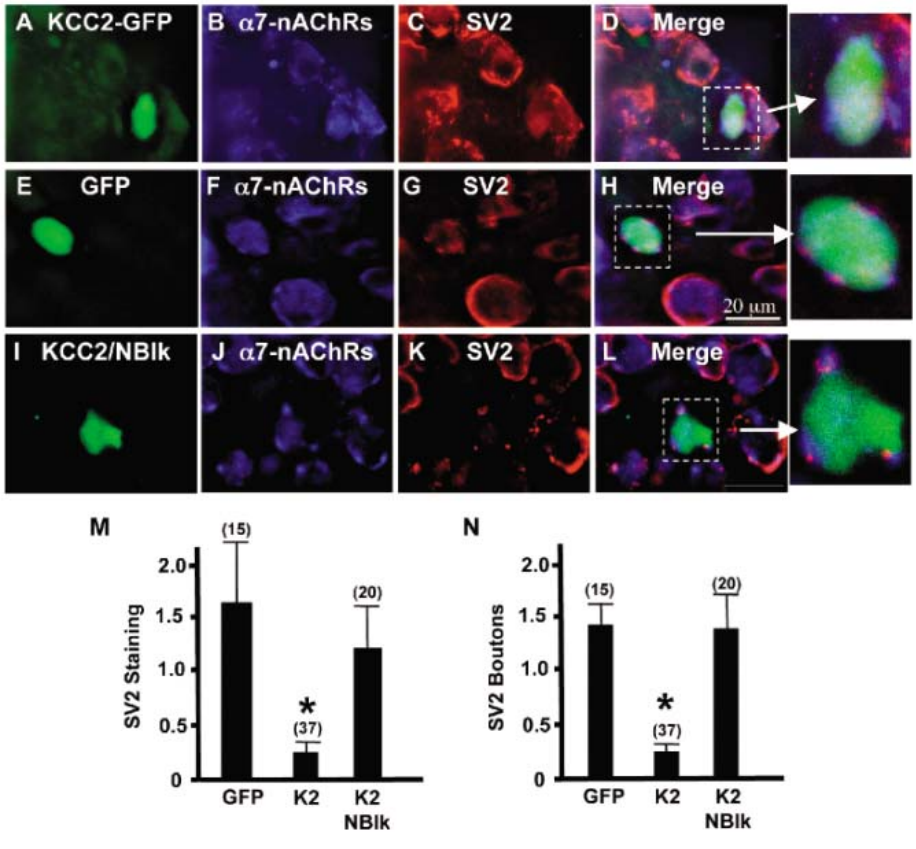

Fig. 4. Early expression of KCC2 in ovo reduces innervation of choroid neurons unless nicotinic activity is blocked. Neurons electroporated at E1.5 in ovo with KCC2-GFP (**A** to **D**), GFP (**E** to **H**), or KCC2-GFP and treated with MLA/DHβE (**I** to **L**) were imaged at E14 in CG sections after staining for α7-nAChRs and SV2 and merging the images (horizontal rows). Arrows indicate blow-ups. The total amount of SV2 puncta staining (**M**) and the number of SV2 puncta (**N**) on the electroporated cell were normalized to that found on adjacent untransfected cells of equivalent size. Scale bar, 20 μm. Values represent mean ± SEM (n = number of electroporated neurons). *, P < 0.05 for (M), P < 0.001 for (N), by ANOVA.

hibition to restrict VGCC participation may be an important determinant of development in many pathways. Prime candidates would be pathways employing calcium-permeable AMPA (*29*) and *N*-methyl-D-aspartate receptors. The timing of the GABAergic switch determines when one set of developmental influences ends and another set begins. This layered sequence of activity may be a common feature where excitation shapes multiple stages of development.

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Supporting Online Material

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Materials and Methods
Figs. S1 to S5
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23 August 2006; accepted 24 October 2006
10.1126/science.1134246

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POSITIONS OPEN

FOREST AND TREE BIOLOGY TENURE-TRACK FACULTY POSITION
University of Victoria, Victoria, British Columbia

The Department of Biology invites applications for a full-time, tenure-track position in forest and tree biology at the **ASSISTANT PROFESSOR** level, affiliated with the Centre for Forest Biology.

Research in the Centre for Forest Biology emphasizes the adaptation of trees and their interactions with the environment. We welcome applicants from all areas of plant biology, especially those working in tree or forest systems, including ecophysiology, population genetics, molecular biology, or genomics. The successful applicant will be expected to develop an independent, innovative, and externally funded research program which complements the research of the Centre, and to participate in teaching at both the undergraduate and graduate levels.

The Department of Biology **(website: http://web.uvic.ca/biology)** and the Centre for Forest Biology **(website: http://web.uvic.ca/forbiol)** provide outstanding resources and opportunities for research, including excellent plant growth facilities and the University of Victoria Genome British Columbia (BC) Proteomics Centre. The Centre for Forest Biology has active collaborations with the Pacific Forestry Centre of the Canadian Forest Service and the BC Ministry of Forests and Range. The University of Victoria is widely recognized for its innovative and responsive programs, interdisciplinary and international initiatives, a diverse and welcoming learning community, and superb location.

The successful applicant will have a Ph.D. with postdoctoral experience demonstrating exceptional research and potential for teaching excellence. Applicants should have a research record in the field of forest and tree biology. Applications must include curriculum vitae, a statement of teaching philosophy and interests, an outline of proposed research, and contact information (name, address, fax, and e-mail) for four referees. Applications should be sent by January 8, 2007, to:

Dr. W. Hintz, Chair
Department of Biology
University of Victoria
P.O. Box 3020, STN CSC
Victoria, British Columbia
Canada
V8W 3N5
Fax: 250-721-7120
E-mail: biochair@uvic.ca

The University of Victoria is an equity employer and encourages applications from women, persons with disabilities, visible minorities, Aboriginal Peoples, people of all sexual orientations and genders, and others who may contribute to the further diversification of the University. The Department and Centre are strongly committed to both excellence and equity, and in consideration of the Department's equity plan, women are especially encouraged to apply. All qualified applicants are encouraged to apply; in accordance with Canadian Immigration requirements, Canadians and permanent residents will be given priority.

POSTDOCTORAL FELLOW position is available immediately in the Department of Immunology/Microbiology at Rush University Medical Center to study the human immune response in the gastrointestinal tract. Our laboratory is involved in evaluating the roles of innate and adaptive immune responses in autoimmunity and infectious diseases. Experience in immunofluorescence and confocal microscopy is required. Sterile technique and cell culture, functional assays that measure humoral and cell mediated immunity, enzyme-linked immunosorbent assay and flow cytometry are highly desired. Qualified candidates should hold a Ph.D. and/or an M.D. Salary is competitive and includes benefits. If interested please e-mail current curriculum vitae to **Dr. Linda Baum (e-mail: linda_l_baum@rush.edu)** or **Dr. Lena Al-Harthi (e-mail: lena_al-harthi@rush.edu), Department of Immunology/Microbiology, Rush University Medical Center, 1735 West Harrison Street, Chicago IL 60612.** *Rush University Medical Center is an Equal Opportunity/Affirmative Action Employer.*

POSITIONS OPEN

ASSISTANT PROFESSOR
Department of Cell Biology and Anatomy

The Department of Cell Biology and Anatomy of the Chicago Medical School, Rosalind Franklin University of Medicine and Science, invites applications for two tenure-track Assistant Professor positions. We seek candidates to join an ongoing expansion of Department and Medical School research faculty. Areas of currently funded research in the Department include the neurobiology of learning and prepulse inhibition, synaptic plasticity in the auditory system, the molecular cell biology of muscle development, cellular trafficking, extracellular matrix, and the cellular dynamics of gene expression. Institutional strengths include neuroscience, structural biology, and membrane transport physiology. The successful applicant is expected to establish a strong, extramurally funded research program, and to contribute to medical and graduate teaching. Available core resources include confocal, live-cell, and electron microscopy facilities, and structural biology and proteomics centers. Information on the University and Department may be found at **website: http://www. rosalindfranklin.edu.**

Applications containing curriculum vitae, statement of research plans, and the names of three references should be sent to: **William Frost, Ph.D., Chair, Department of Cell Biology and Anatomy, The Chicago Medical School, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Road, North Chicago, IL 60064.** Alternately, materials may be submitted via e-mail to **e-mail: william.frost@rosalindfranklin.edu.** Review of applications will begin immediately and will continue until the positions are filled.

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FACULTY POSITION IN STRUCTURAL BIOLOGY
The University of Georgia

The Department of Biochemistry and Molecular Biology at the University of Georgia invites applicants for a tenure-track **ASSISTANT PROFESSOR** position in structural biology. Applicants from any area of structural biology are welcome and can build on, or complement existing strengths at the University of Georgia in X-ray crystallography, nuclear magnetic resonance, and mass spectrometry. The University of Georgia provides a highly interdisciplinary and supportive environment with opportunities for development of innovative collaborations with researchers in many areas including developmental biology, infectious diseases, and glycobiology. The position includes a competitive salary, excellent laboratory space, and a generous startup package. The successful candidate will be expected to develop a strong extramurally funded research program and contribute to teaching in the Department of Biochemistry and Molecular Biology.

Applications received by January 15, 2007, are assured full consideration. Please e-mail curriculum vitae, research and teaching statements, the names of three references, and up to three publications (all in PDF format) to **e-mail: shajduk@bmb.uga.edu.** Electronic letters of recommendation are acceptable if followed by an original.

Letters of recommendation should be mailed to:

Dr. Stephen L. Hajduk
Professor and Head
The University of Georgia
Department of Biochemistry and Molecular Biology
Fred C. Davison Life Sciences Building
Athens, GA 30602

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Positions @ NIH
THE NATIONAL INSTITUTES OF HEALTH

Department of Health and Human Services
National Institutes of Health
Tenure-Track Position

The Division of Intramural Research, National Institute on Deafness and Other Communication Disorders (NIDCD), located in Bethesda, MD, is seeking a tenure-track scientist to establish an independent research program to study molecular and/or cellular mechanisms of hearing and balance. We welcome applications from candidates with a wide range of expertise. Preference will be given to candidates whose experimental approaches complement those of our existing strong programs in the genetics, development and cell biology of hearing. The successful candidate will join a dynamic group of scientists in a growing intramural program that is at the forefront of research on communication disorders.

The NIDCD offers an exceptional working environment including well-equipped research laboratories and numerous opportunities for collaboration. Candidates for this position must possess a Ph.D. and/or M.D., post-doctoral experience, and an outstanding publication record. Salary is commensurate with education and experience.

Please submit a curriculum vitae including bibliography, three reprints of recent relevant publications, statement of research interests, an outline of your proposed research, and the names and addresses of three references to: **Ms. Trudy Joiner, Office of the Scientific Director, NIDCD, 5 Research Court, Room 2B28, Rockville, MD 20850 (joinert@nidcd.nih.gov)**. Applications will be accepted until **December 15, 2006**.

Postdoctoral Fellowship Position

A five year post-doctoral fellowship is currently available on a competitive basis at the NCI for a productive, highly-motivated, and energetic individual. The opening is in a laboratory studying T cell tolerance to tumor antigens. Opportunities exist to study cellular and molecular aspects of T cell responses to tumor antigens as well as to study inflammation and cancer using contemporary murine models. A dynamic research environment and outstanding resources are available for enthusiastic individuals. Requirements include an M.D., Ph.D., or equivalent degree and experience in Immunology research. Candidate must have excellent verbal, written, communication and organizational skills and an ability to handle multiple projects simultaneously. More information on research projects can be found at **(http://ccr.cancer.gov/staff/staff.asp?profileid=7740)**. Interested individuals should send their CV and a letter of research interests to **Dr. Arthur Hurwitz: hurwitza@ncifcrf.gov.**

POSTDOCTORAL FELLOW

Systems Neuroscientist/Drug Abuse/ Animal fMRI Neuroimaging

The Department of Health and Human Services (DHHS), National Institutes of Health (NIH) is recruiting for a neurobiologist who is interested in joining an interdisciplinary group of scientists in the Neuroimaging Research Branch, Intramural Research Program (IRP), National Institute on Drug Abuse (NIDA). The mission of the group is to enhance our understanding of fundamental brain mechanisms of drug abuse. The successful candidate will join a team of neurobiologists and MR physicists using fMRI and other MRI techniques to study the neurobiology of abused drugs in rodent and non-human primate models. Experiments are performed on a research dedicated, 9.4T Bruker MRI scanner. Some projects are part of a 'Bench to Bedside' collaboration with the University of Pennsylvania School of Medicine. The successful candidate must possess a Ph.D. in Neuroscience, Physiology, Pharmacology, or a related field. Experience in small animal neuroscience research and/or fMRI neuroimaging is desirable.

Interested applicants must submit a CV, a statement of research interests and goals, three letters of recommendation, and a copy of the doctoral degree (if in a foreign language, include a certified English translation). Send applications to: **Dr. Elliot Stein, Neuroimaging Research Branch, NIH/NIDA/ IRP, 5500 Nathan Shock Drive, Building C, Room 383, Baltimore, MD 21224; or e-mail estein@intra.nida.nih.gov**. For inquiries: **(410) 550-1440 x 338 (voice)**.

Department of Health and Human Services
National Institutes of Health
Clinical Center

Tenure-track Physician
Clinical Center/Nuclear Medicine Department

This position is located in The Warren G. Magnuson Clinical Center, Nuclear Medicine Department (NMD).

We are seeking a research-oriented physician for a possible tenure-track position. An M.D. or M.D. /PhD with U.S. Nuclear Medicine Board certification and CT training is needed to provide diagnostic and therapeutic nuclear medicine procedures as well as to participate in clinical research protocols of the NIH Intramural Program. U.S. citizenship or permanent residency status is required.

Please submit your curriculum vitae, bibliography, and a letter describing your clinical, research, and management experience to: **Mrs. Veronica Olaaje, HR Specialist, DHHS, NIH, OD/CSD-E, 2115 E. Jefferson Street, Rm. 2B209 MSC-8503, Bethesda, MD 20892-8503. Phone: 301-435-4748. Email: volaaje@mail.nih.gov**.

Salary is commensurate with experience. This appointment offers a full benefits package (including retirement, health, life and long term care insurance, Thrift Savings Plan participation, etc.). Application packages should be submitted as early as possible, but no later than **December 31, 2006**.

Selection for this position will be based solely on merit, without discrimination for non-merit reasons such as race, color, religion, sex, national origin, politics, marital status, sexual orientation, physical or mental handicap, age or membership or non-membership in an employee organization.

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Senior Investigator (Tenured), Laboratory of Immunoregulation
National Institute of Allergy and Infectious Diseases
National Institutes of Health (NIH)

The National Institute of Allergy and Infectious Diseases (NIAID), Division of Intramural Research (DIR) is recruiting a Senior Investigator (tenured) in the Laboratory of Immunoregulation (LIR), Immunopathogenesis Section. The NIAID is a major research component of the NIH, the Department of Health and Human Services (DHHS).

The LIR is seeking a scientist to develop an independent research program on the study of the immunopathogenesis of HIV disease with a special interest in natural antiviral and immunomodulatory factors, particularly chemokines and other molecules with HIV-suppressive activity. He or she will also attempt to develop novel therapeutic or prophylactic strategies against HIV based on such natural factors. The ideal candidate will have an M.D. or Ph.D. degree with a specialization in microbiology, immunology and/or infectious diseases and have considerable experience in HIV virology and immunology.

The scientist selected for this position will receive independent and committed resources to conduct laboratory research; these include space, technical and postdoctoral fellow support, and an allocated annual budget to cover services, supplies and salaries. Additional resources may be provided for the development of clinical research related to HIV infection. A senior investigator in the DIR, NIAID, is equivalent to a full tenured professor in a university or medical School. Salary will be based on the individual's qualifications and experience. Other incentives may be available.

Interested candidates may contact **Marybeth Daucher via e-mail at mdaucher@niaid.nih.gov** for additional information about the position.

Application Process: To apply for the position, candidates must submit a curriculum vitae, bibliography, and detailed statement of research interests (1-2 pages). In addition, three letters of recommendation must be sent directly from the referees. All materials may be sent via e-mail to **Felicia Braunstein at braunsteinf@niaid.nih.gov** or by U.S. mail to: **Ms. Felicia Braunstein, DIR Committee Manager, LIR Search Committee, 10 Center Drive MSC 1349, Building 10, Rm 4A-30, Bethesda, Maryland 20892-1349**. Complete applications **MUST** be received by **January 5, 2007**. Please note search **#003** when sending materials. For additional information on this position and instructions on submitting your application, please see our website at **http://www.3.niaid.nih.gov /about/working/joblistings/open_positions.htm**. All information provided by applicants will remain confidential and will only be viewed by authorized officials of the NIAID.

Staff Scientist (Core Laboratory)

The National Institute of Allergy and Infectious Diseases (NIAID), a major research component of the NIH and the Department of Health and Human Services, is recruiting for a Staff Scientist (Core Laboratory) in the Respiratory Viruses Section, Laboratory of Infectious Diseases (LID). LID has an active vaccine development program to generate live attenuated virus vaccines for flaviviruses including the four dengue, West Nile encephalitis, St. Louis encephalitis, and Tick-borne encephalitis viruses and respiratory viruses including the three parainfluenza viruses, two respiratory syncytial viruses, and the human metapneumoviruses. Vaccines are also being developed against viruses of interest to biodefense.

Responsibilities: 1) generate documents constituting the Investigational New Drug Application (IND) for the vaccines being developed; 2) work closely with members of the Sponsor of the IND, another unit of the Intramural program of NIAID, to generate final IND documents for submission to the FDA; 3) coordinate efforts of LID staff involving vaccine manufacture and preclinical testing of the vaccine candidates; and 4) organize the response of NIAID to the comments of the FDA regarding IND submissions.

The successful individual will ideally possess an M.D. or Ph.D. degree and have experience with IND preparation for infectious agents, but individuals without one of these degrees will also be considered if they have extensive experience in the field. Experience with generation of investigational vaccines, especially cDNA derived vaccines, and testing of investigational vaccines in animals and human subjects is desired. Salary range is $73,178 - $159,657 and is commensurate with research experience and accomplishments.

Please send CV/Bibliography and three references to **Dr. Alexander Schmidt, Bldg. 50, Room 6511, 50 South Drive, MSC 8007, Bethesda, MD 20892-8007**. Applications must be received by **January 5, 2007**. For additional information on this position, contact **Dr. Alexander Schmidt at schmidta@niaid.nih.gov**.

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FACULTY POSITIONS IN NEUROSCIENCE/NEUROLOGY

Faculty positions at all levels are available in the Departments of Neuroscience/Neurology at the Albert Einstein College of Medicine for individuals applying techniques of molecular genetics in various model organisms to study different areas of normal neural development and/or diseases of the nervous system. Possible areas of concentration include neuronal and glial specifications, stem and progenitor cell biology, synaptogenesis, pattern formation, axonal guidance, cell-cycle regulation, developmental and pathological cell death, neural repair mechanisms, genetics of neurodegenerative diseases and epigenetic control of gene-environmental interactions during neurological development and in health and disease.

This is part of an ambitious recruitment effort aimed at significantly increasing the complement of interdisciplinary neuroscience investigators at the Rose F. Kennedy Center for Research in Mental Retardation and Developmental Disabilities. It is expected that the successful candidates will have established or will develop independent research programs that will provide essential links in the long-standing tradition of academic excellence in neuroscience research at Einstein.

Albert Einstein College of Medicine (AECOM) is a major biomedical institution that maintains a strong focus on basic science research and interdisciplinary collaborations. Of particular relevance to this search are the extensive opportunities for interactions with faculty members in the Departments of Molecular Genetics, Developmental and Molecular Biology, Cell Biology, Anatomy and Structural Biology, Physiology and Biophysics, Pathology, and Psychiatry, as well as those to be housed in the Price Center for Genetic and Translational Medicine, a new research building on campus that will open in early 2008.

This position offers the opportunity to mentor graduate students with a strong interest in basic science and translational research. In addition to the approximately 400 PhD students that are actively pursuing graduate studies, Einstein maintains one of the largest and most highly regarded MD/PhD programs. Further, state-of-the-art genomics, epigenomics, proteomics, and neuroimaging facilities, as well as extensive dedicated mouse housing are available to all members of the Einstein community **http://www.aecom.yu.edu.**

The Albert Einstein College of Medicine is located in a pleasant residential section of the Bronx with easy access to Manhattan, Westchester County and other communities of the New York Metropolitan area. Applicants should submit their curriculum vita, a short description of future research plans, and have at least three letters of reference forwarded to the Neuroscience/Neurology Search Committee care of: **Ms. Maura Gabriele, Kennedy Center 906, AECOM, 1410 Pelham Pkwy., Bronx, NY 10461.** The deadline for receipt of application is **Feb 1, 2007.** EOE.

ALBERT EINSTEIN COLLEGE OF MEDICINE
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Faculty Positions
Plant Biology and Microbiology

Hunan University (Changsha, China) seeks candidates for 2 Professor positions immediately, in the area of plant biology and microbiology, at the Bioenergy and Biomaterial Research Center (BBRC) jointly established recently by the Hunan University and the Chinese Academy of Agricultural Sciences. Successful candidates are expected to develop independent research programs aimed at understanding basic molecular mechanisms governing development or metabolisms in plants or microbials. A start-up fund of up to $0.5 million is provided for each position.

Qualified candidate should electronically submit: (1) CV and reprints of publications, (2) research accomplishments and detailed future research plan, to **xuhongy@gmail.com**, by **February 1, 2007**. In addition, 3 letters of reference should be sent directly to: **BBRC Search Committee, c/o Hongyun Yang, Department of MCDB, UCLA, Los Angeles, CA90095-1606**, Email: **xuhongy@gmail.com**. BBRC will have additional positions opening in the next two years. Interested candidates may also apply after the above deadline for future considerations.

TRINITY COLLEGE DUBLIN
The University of Dublin

www.tcd.ie/vacancies

Trinity College is recognised internationally as Ireland's premier university and is the only Irish university to rank in the top 100 world universities (78th) and amongst the top 50 European universities (25th). We are recruiting world class leaders in research and education to advance our research strengths, develop our fourth level graduate education and build on our excellence in third level undergraduate education. Our strategic priorities of research and education are also aligned with contributing to the national goal of fostering Ireland's cultural and economic vibrancy.

School of Biochemistry and Immunology
Chair of Biochemistry (1960)

The School of Biochemistry and Immunology at Trinity College Dublin invites applications for the Chair of Biochemistry (1960) tenable from 1 June 2007 or as soon as possible thereafter.

The School seeks an individual who will provide innovative and energetic leadership and has a strong commitment to academic excellence at a major research university. The successful candidate will be an internationally recognised scholar in any area of biochemistry and an academic leader of the highest calibre with a proven track record of research and teaching.

The appointee will join a dynamic team of researchers whose interests span all areas of biochemistry. The research interests of the candidate will be expected to complement those currently in the School of Biochemistry and Immunology and to support the School's undergraduate and postgraduate teaching programmes.

The successful candidate will be expected to take a leadership role in the School and will serve a term as Head of School and/or Head of the Discipline of Biochemistry in due course, in accordance with College regulations.

Information about the School of Biochemistry and Immunology can be found at http://www.biochemistry.tcd.ie/. Further particulars of the appointment, including the application procedure and details of salary may be obtained from:

Michael Gleeson, Secretary to the College, West Theatre, Trinity College, Dublin 2

Telephone: +353-1-896-1722, Fax: +353-1-671-0037, Email: moya.thompson@tcd.ie

to whom formal applications may be sent to arrive by the preferred closing date of noon on Friday 19 January 2007.

Trinity College is an equal opportunities employer.

Yale School of Public Health
Yale University School of Medicine
Assistant or Associate Professor
Infectious Disease Ecologist

A tenure track faculty position at the Assistant or Associate Professor level is available for an infectious disease ecologist. The position is designed to bridge the academic and intellectual gap between ecology and medical epidemiology by fostering interdisciplinary research and training. Opportunities exist for collaborations with faculty at the Yale School of Medicine, Yale School of Forestry and Environmental Studies, and Departments of Ecology and Evolutionary Biology, and Geology and Geophysics. The position is partially funded by the Yale Institute for Biospheric Studies through the newly formed Center for EcoEpidemiology.

Candidates should have a Ph.D. in ecology and postdoctoral experience in infectious diseases of humans, animals or plants, and would be expected to develop an extramurally funded research program in disease ecology, and teach an interdisciplinary graduate course in the School of Public Health/Department of Epidemiology and Public Health. For full consideration, applicants should submit a statement of research interests, a complete curriculum vitae, and the names of five references by **February 1, 2007** to: **Durland Fish, Search Committee Chair, Yale School of Public Health, Yale University School of Medicine, P.O. Box 208034, New Haven, CT 06520-8034;** Email: **durland.fish@yale.edu.**

Yale University is an Affirmative Action/Equal Opportunity Employer. Men and women of diverse racial/ethnic backgrounds and cultures are encouraged to apply.

UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

School of Molecular & Cellular Biology and College of Medicine

The **School of Molecular and Cellular Biology** <http://www.life.uiuc.edu/mcb/> , the **College of Medicine** <http://www.med.uiuc.edu/> and the **Institute for Genomic Biology** <http://www.igb.uiuc.edu/>, at the University of Illinois at Urbana-Champaign invite applications for **multiple tenure track faculty positions** as described below. All of these positions require a Ph.D. and/or M.D. degree and postdoctoral experience. The starting date for these positions is August 16, 2007; however, this date is negotiable. We offer the opportunity to join a rapidly growing group of outstanding biological scientists on a campus that provides a highly interactive, interdisciplinary research environment and state-of-the-art research support facilities. The University of Illinois at Urbana-Champaign has added significant faculty strength in the biological sciences over the last several years and we anticipate additional hires in these and related areas in the future. Each of these positions offers excellent laboratory facilities, substantial start-up funds, and the opportunity to work with outstanding graduate students. The UIUC campus offers a wide range of state-of-the-art research support facilities, including mass spectrometry, NMR, X-ray crystallography, micro- and nanoscale fabrication and analysis, the Roy J. Carver Biotechnology Center, the W. M. Keck Center for Comparative and Functional Genomics as well as facilities for proteomics, metabolomics, immunology, and flow cytometry. A transgenic mouse facility will open for operation this fall. Superb resources for computational biology are available on campus at the National Center for Supercomputing Applications and the NIH Resource for Macromolecular Modeling and Bioinformatics. The Institute for Genomic Biology a new 186,000 square foot facility devoted to biological research, will open this fall.

Salaries for these positions are commensurate with experience and are competitive. Urbana-Champaign offers the residential advantages of a medium-sized university city, excellent cultural opportunities, and easy access to Chicago, St. Louis, and Indianapolis.

Biochemistry/Institute for Genomic Biology – Rank Open
The Institute of Genomic Biology (IGB) and the Department of Biochemistry invite applications for one or two tenure-track positions at the Assistant, Associate, and Full Professor levels in the areas of **(1) protein engineering and molecular recognition, (2) structural biology and x-ray crystallography**. Candidates at the Assistant Professor level will be expected to establish a high-quality, externally funded research program and have a commitment to outstanding graduate and undergraduate teaching. Candidates at higher levels will be expected to present evidence of outstanding research accomplishments. Appointees in the IGB will also help unite an interdisciplinary team comprised of experts in mass spectrometry, fluorescence spectroscopy, and surface science to help establish next generation technologies focused on central issues in modern cell biology and human disease.

Cell Biology - Rank Open
The Department of Cell and Developmental Biology < http://www.life.uiuc.edu/cdb/> invites applications from outstanding candidates whose research addresses fundamental questions of modern cell biology. Applications for positions at the Assistant, Associate and Full Professor levels will be considered, and highly qualified scientists at these levels are encouraged to apply. Appointment at the Assistant Professor level requires evidence of outstanding research potential. Appointees at this level will be expected to develop a vigorous, independently funded research program. Appointment at higher levels requires evidence of outstanding research accomplishments. Applicants at all levels will be responsible for undergraduate, graduate or medical cell biology teaching.

Microbiology/Institute for Genomic Biology – Rank Open
The Department of Microbiology and The Institute of Genomic Biology at the University of Illinois-Urbana Champaign seeks applications for an Open Rank position in the field of microbial secondary metabolism and/or antibiotic biosynthesis. The successful candidate will be expected to direct an active research program involving the use of microbiology, genetics, molecular biology, genomics, biochemistry or chemistry to address problems broadly relating to the discovery and biosynthesis of microbially produced bioactive compounds. The chosen candidate will join an active research group at the University of Illinois engaged in research towards antibiotic discovery, design and development, which currently includes members of the Departments of Chemistry, Microbiology, Biochemistry and Chemical and Biomolecular Engineering.

Molecular and Integrative Physiology – Assistant Professor
The Department of Molecular and Integrative Physiology seeks an exceptional candidate for a tenure track position in Neuroendocrinology. The successful applicant will have an established record of research excellence that addresses fundamental questions related to the function of complex systems. M.D./Ph.D. physician-scientists are encouraged to apply. We are particularly interested in research that complements departmental/campus strengths in reproductive biology, neuroscience, human behavior, metabolic systems and nutrition. Teaching at the graduate and undergraduate levels is expected.

Pharmacology – Assistant Professor
The Department of Pharmacology in the College of Medicine and the School of Molecular and Cellular Biology invite applications for a full-time tenure-track faculty position at the Assistant Professor level. M.D./Ph.D. physician-scientists are particularly encouraged to apply. Applicants should be qualified to teach basic principles of pharmacology to second year medical students in the College of Medicine. Appointees will be expected to develop a vigorous, independently-funded research program that addresses contemporary questions in pharmacology or related basic biomedical sciences, including genomic approaches such as pharmacogenetics or pharmacogenomics. Applicants may also be considered for an appointment in Chemical Biology in the School of Chemical Sciences <http://www.scs.uiuc.edu/>, if appropriate.

Applications should clearly indicate the position(s) applied for and should be submitted to: School of Molecular and Cellular Biology Search, University of Illinois at Urbana-Champaign, 393 Morrill Hall, 505 S. Goodwin Ave., Urbana, IL 61801. The application must include a curriculum vitae with a complete list of publications, a concise summary of past research accomplishments, and future research plans. Please arrange to have no fewer than three letters of recommendation sent to the same address.

Electronic submissions as pdf or Microsoft Word files are encouraged and should be sent to mcbsearch07@life.uiuc.edu. To ensure full consideration, applications must be received by January 3, 2007. Interviews may be conducted before the closing date but no hire will be made until after the search is closed.

The University of Illinois at Urbana-Champaign is an Affirmative Action, Equal Opportunity Employer.

IN 2007

CNRS IS RECRUTING

MORE THAN 400 TENURED RESEARCHERS IN ALL SCIENTIFIC FIELDS*

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This recruitment campaign is open to junior and senior researchers from all over the world. One of the major objectives of this campaign is to encourage international scientists to apply to CNRS.

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›› numerous large-scale facilities
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Application deadline: January 15th 2007

www.cnrs.fr

CNRS CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Faculty Position in the Institute of Marine Affairs (NSYSU), Taiwan

Institute of Marine Affairs (IMA) and Department of Marine Environment and Engineering (MEE) of National Sun Yat-sen University at Kaohsiung City, Taiwan, are seeking candidates for five tenure-track positions at all levels. Four staff members for IMA are sought with specialization in marine policy and law, fishery resource management, marine environmental studies, or coastal zone management. One staff member for MEE must have a major in environmental planning and management. IMA offers master degree and is newly formed at 2005. Candidates must hold a Ph.D. with proven track records of accomplishments. English speaking candidates without Mandarin knowledge are welcome to apply.

Applications should include, a curriculum vitae, selected reprints and publication lists, statements of teaching and research interest, two recommendation letters (at least), before **January 15, 2007** (or until the position is filled). All correspondence shall be sent to: **Prof. Chiu L. Chou, Director of Institute of Marine Affairs, National Sun Yat-sen University, 70 Lien-Hai Road, Kaohsiung City, Taiwan**, or Email to: **syvia@staff.nsysu.edu.tw**. Applicants for MEE position please send to **Prof. Chonlin Lee**, or Email to: **linnohc@mail.nsysu.edu.tw**.

Assistant or Associate Professor Level Tenure-Track Appointments

Harvard Medical School and Children's Hospital, Boston

We are seeking outstanding scientists working in the broad area of mucosal biology, innate and acquired host defense, or development and maintenance of the intestinal epithelium and related epithelial barriers. Candidates with innovative scholarship and expertise in cell and molecular biology or immunology are encouraged to apply.

Applicants must possess a PhD or MD and appropriate post-doctoral research experience. Candidates will be expected to establish an extramurally-funded research program or to have an established program in place. Additional duties may include teaching at the graduate and postgraduate levels or clinical practice. Physician-scientists may be trained in disciplines other than pediatrics. The new faculty member will join the Gastrointestinal Division and the Harvard Digestive Diseases Center directed by Associate Professor Wayne I. Lencer and will be appointed at Harvard Medical School. Joint appointments with other Departments will be considered.

Send Curriculum Vitae, names of three individuals who would provide letters of reference, and a one- to two-page synopsis highlighting past work and indicating 2-3 important papers, current research interests, and new directions.

The application should be sent electronically to Alicia Christensen at Alicia.Christensen@childrens.harvard.edu.

Children's Hospital and Harvard Medical School are Affirmative Action/Equal Opportunity Employers.

Children's Hospital Boston

UAMS
COLLEGE OF MEDICINE
UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

CHAIR

DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

The College of Medicine at the University of Arkansas for Medical Sciences (UAMS) invites applications and nominations for the position of Chair of the Department of Microbiology and Immunology. Candidates must have strong leadership experience in research, administration and education, evidence of scholarly accomplishments, and a strongly funded research program transportable to the UAMS College of Medicine. The successful candidate will be expected to foster the growth of innovative, high-quality research and educational programs within the department, and build intra- and interdepartmental research and training programs leading to collaborative grants. Responsibilities include leadership of an academic department to serve the University's four-fold mission of teaching, healing, searching and serving. The Department of Microbiology and Immunology has 21 full-time faculty members. It hosts active, NIH-funded research programs in infectious disease, pathogenic bacteriology and virology, cellular and molecular immunology, and tumor immunology. The environment nurtures scholarly, university-based research and collaborative relationships.

For more information about the UAMS and its College of Medicine, please visit our website at **www.uams.edu**. This is an exceptional opportunity for a leader with the vision to bring a strong department to the next level of excellence.

Applications, nominations, and requests for information may be sent to: **Nancy J. Rusch, Ph.D., Chair, Search Committee for the Microbiology and Immunology Chair, Department of Pharmacology and Toxicology, The College of Medicine, University of Arkansas for Medical Sciences, 4301 W. Markham Street, Slot 611, Little Rock, AR 72205; Phone: (501) 686-8038; Email: nrusch@uams.edu.** Applicants submitting a letter of interest should include a curriculum vitae.

UAMS is an Equal Opportunity Employer, promoting workplace diversity.

Institute for Basic Biomedical Sciences
Johns Hopkins University School of Medicine

Faculty Positions

The Institute for Basic Biomedical Sciences at The Johns Hopkins School of Medicine has embarked on a major new initiative to create cross-disciplinary centers that provide an interactive research environment for Investigators with a variety of scientific approaches and overlapping scientific interests. Faculty recruited to the centers will reside in new laboratories in the existing Basic Science research complex and receive primary appointments in an existing Department in the School of Medicine.

Center for Cell Dynamics

The Center for Cell Dynamics focuses on the analysis of spatially and temporally regulated molecular events in living cells, tissues and organisms. We study a variety of essential cellular behaviors such as cytokinesis, cell motility, and neural plasticity, and cut across traditional departmental boundaries with the common goal of monitoring dynamic biochemical reactions in real time with the highest possible spatial resolution. The center is recruiting new faculty who will develop and apply new experimental approaches in a collaborative, interactive, and interdisciplinary environment.

Center for Epigenetics

Members in the Center for Epigenetics seek to understand the mechanisms by which cellular information other than the DNA sequence modulates gene expression, development and disease. The premise of the Center is that insights will come from interactive and collaborative efforts across disciplines, including biochemical and structural studies of chromatin and DNA modifications, and the epigenetics of humans and model organisms. We seek new basic science faculty interested in pioneering this area. A strong technological and statistical foundation is provided by an NIH funded Center of Excellence in Genome Sciences.

Center for Metabolism and Obesity Research

The mission of the Center for Metabolism and Obesity Research (CMOR) is to study and support integrative research in the field of metabolism and systems biology. Our objective is to advance our understanding of the biological mechanisms that regulate metabolism and how they are dysregulated in attendant disorders, such as obesity and diabetes. CMOR seeks to recruit faculty interested in applying in vitro and in vivo models to further our understanding of the regulation of energy sensing, nutrient sensing, and endocrine responses and how these processes are altered by disease. Our goal is to create a multidisciplinary and collegial center.

Center for Sensory Biology

The Center for Sensory Biology seeks to understand the fundamental processes underlying the primary senses – vision, touch (including pain), chemosensation (taste and smell) and hearing. Research within the Center is based on the recognition that sensory systems use conserved biological processes for signaling, adaptation and modulation, and for protection from injury, environmental insult, and degeneration. The Center is recruiting new faculty interested in working on diverse sensory systems and applying new tools and experimental approaches in a collaborative, interactive and interdisciplinary environment.

Applicants should submit their application by January 15, 2007 via email (IBBScenters@jhmi.edu) and include a CV, research plan, names of three references and up to three publications (all in pdf format). Indicate in the subject line which center should consider your application. Please arrange for letters of recommendation on your behalf be sent to the same email address. Applicants will only be considered by one of the centers.

The Johns Hopkins University is committed to diversity and equality in education and employment and encourages applications from under-represented groups

The Rangos Building houses the new Centers for interdisciplinary research in the Institute for Basic Biomedical Sciences and is part of the Science + Technology Park at Johns Hopkins.

UNIVERSITY AT ALBANY
State University of New York

Tenured Faculty Positions in Cancer Genomics

The University at Albany invites scientists with demonstrated excellence in cancer research to apply for two tenured faculty positions (Associate or Full Professor level) in the Gen*NY*Sis Center for Excellence in Cancer Genomics (**http://www.albany.edu/cancergenomics/**) . Successful applicants will be part of the new Chancellor's Empire Innovations Program, which seeks to recruit outstanding faculty to the New York State University system. They will be housed in the new 120,000 sq. ft. Cancer Research Center which is part of the University's $150,000,000 expansion in the Life Sciences and offers fully staffed, state-of-the-art core facilities in genomics, proteomics, bioinformatics, microarray, flow cytometry, imaging, and cell culture and transgenesis. Successful applicants will interact with a group of exceptional young investigators studying various aspects of cancer genomics. Startup packages, salary, and benefits are highly competitive.

The first position is in the general area of environmental carcinogenesis. The second position is open to candidates in all areas of cancer genomics. Researchers using systems biology approaches to their research are especially encouraged to apply. Academic appointment will be in the Department of Biomedical Sciences, or the Department of Environmental Health Sciences, of the University's School of Public Health (**http://www.albany.edu/sph/**). Both Departments are closely associated with the Wadsworth Center, the research-intensive laboratory of the New York State Department of Health. Scientists in the School of Public Health and the Wadsworth Center study public health issues, from drug resistance to emerging infections and environmental toxicants. They also investigate basic biological processes that contribute to human health and disease. The Albany area also has several other institutions with strong research programs related to cancer genomics including Rensselaer Polytechnic Institute, Albany Medical College, the Pharmaceutical Research Institute, and the Ordway Research Institute and thus, there is outstanding potential for research collaborations.

As the capital city of New York State, Albany provides outstanding cultural and recreational opportunities. It maintains a vibrant small-city life style while being within easy commute (3 hours) to major metropolitan centers including New York City, Boston and Montreal.

Applicants must submit, via email, a curriculum vitae, and a succinct statement of current and future research interests. These positions require a Ph.D., M.D. or equivalent degree in Biological, Biomedical, or Life Sciences from a college or university accredited by a U.S. Department of Education or internationally recognized accrediting organization. Applicants must address in their applications their abilities to work with and instruct a culturally diverse population.

Interested individuals should submit materials to: **Lynda Peckowitz, University at Albany, One Discovery Drive, Executive Suite 304, Rensselaer, NY 12144-3456, E-mail: genomics@albany.edu**

The University at Albany is an AA/EO/IRCA/ADA employer.

The **Department of Surgery** at the **University of Pennsylvania's School of Medicine** seeks candidates for an Assistant or Associate Professor position in the tenure track. Rank will be commensurate with experience. The successful applicant will have experience in the field of experimental pathology with a focus on smooth muscle physiology/pharmacology and cell/molecular biology or biochemistry. Responsibilities include targeted research in urothelial biology, smooth muscle physiology, interstitial cystitis and tissue and cell engineering to correct urologic disorders, as well as teaching of medical students and residents doing research rotations in the Urology laboratories. Applicants must have an M.D and/or Ph.D or equivalent degree.

This position, which will be based in the Division of Urology, will include teaching and research duties only, with no patient care responsibilities. The successful candidate will have demonstrated potential for establishing a vigorous independent research program in the cellular/molecular basis of diseases of the lower urinary tract. Preference will be given to candidates with experience in basic urological research and a track record for obtaining research grants.

Please submit curriculum vitae, a letter of interest, and References to: **Alan J. Wein, MD Chief, Division of Urology, c/o Peter Atherton, Univ. of Pennsylvania Sch. of Med., 3400 Spruce St., 4029 Maloney, Philadelphia, PA 19104-4283; athertop@uphs.upenn.edu**.

The University of Pennsylvania is an Equal Opportunity, Affirmative Action Employer. Women and minority candidates are strongly encouraged to apply.

Opportunities for EU Scientists to apply for financial support for field work at the Abisko Scientific Research Station in the Swedish Subarctic

The Abisko Scientific Research Station has received the EU-grant ATANS (Access To Abisko Naturvetenskapliga Station) within the EU Transnational Access Programme (FP6 Contract N° 506004) for the period 2005 – 2008. This grant will financially support travel and accommodation costs at the Abisko Station for scientists in EU-countries outside Sweden as well as scientists from Associated States.

Proposals are invited from established and young researchers that relate to research on the natural environment (geosphere, biosphere, hydrosphere and cryosphere) of the Abisko area. Some specific scientific areas are particularly encouraged, for example, projects that integrate or link existing research groups (e.g. IPY-International Polar Year projects), projects led by scientists from new EU-member states, projects that focus on environmental processes during winter and projects by first-time users and research groups.

The Abisko Station is a unique, long-established, modern and comprehensive infrastructure situated in a wilderness area (68º21'N, 18º49'E) about 200 km north of the Arctic Circle within a range of terrestrial and freshwater environments. The Station is easily accessible by road, rail and air and it provides a unique milieu of international environmental expertise.

Further information and application details can be found at:
www.ans.kiruna.se

FIU
Florida International University

College of Engineering and Computing

FLORIDA WORLD CLASS SCHOLARS in Nanotechnology and Bionanotechnology

Florida International University is seeking applications for two senior level faculty positions in nano technology, made possible by the Florida 21st Century World Class Scholars Program. Successful candidates are expected to develop world class research programs at FIU's new Motorola Nanofabrication Research Facility, the leading centralized nano-research facility in the State of Florida. One candidate will be considered for Director of the Facility and the Advanced Materials Engineering Research Institute, and the other candidate will lead the research efforts in bionanotechnology. Applicants will be considered for appointments in an appropriate department, or joint appointments. Areas of particular interest are carbon nanotube and nanowire materials processing, nanoelectronics, nanosensor and biosensor development, and biodetoxification. Applicants should have a doctoral degree in engineering, science or a related discipline; a substantial record of scholarly work, extramurally funded research; and a demonstrated ability to lead large research programs, develop new intellectual property, and collaborate with industry on applications with commercial potential.

FIU has a student body of over 38,000 and is located in Miami, Florida, a diverse metropolitan area with a strong biomedical industry. It is ranked as a Research University in the High Research Activity category of the Carnegie Foundation's classification system. Research in the area of nanodevices and systems is supported by multi-million dollar grants from Federal agencies and industry. See **http://www.eng.fiu.edu**.

Send nominations or applications by e-mail to: **Richard T. Schoephoerster**, Chair, Search and Screen Committee, **bmeinfo@fiu.edu**. Application review begins **December 1, 2006**, continuing until the position is filled. Application materials should include curriculum vitae, teaching and research experience, a vision statement, and a list of at least five references. For more information, e-mail **schoepho@fiu.edu**.

FIU is a member of the State University System of Florida and an Equal Access/Equal Opportunity Employer and Institution.

Tenure-Track Faculty Position in Marine Science

The University of Texas at Austin Department of Marine Science and Marine Science Institute invite applications for a faculty position in marine science. All fields will be considered, but areas of particular interest include estuarine and/or coastal ecology with an emphasis on benthos or nekton. Candidates must have a Ph.D. degree at the time of appointment. Postdoctoral experience, a strong research and publication record, and an emphasis on field research are preferred. The position, based at the Marine Science Institute (**www.utmsi.utexas.edu**) in Port Aransas, TX, includes 9 months of annual salary support for research and teaching activities. The Institute manages the newest site in the National Estuarine Research Reserve system, which includes 185,000 acres of subtropical estuarine habitats.

Each applicant should send a PDF file containing a statement of research and specific teaching interests (3 pages maximum) and curriculum vitae to **facsearch@utmsi.utexas.edu**, and have at least three letters of recommendation mailed to:

Search Committee Chair
The University of Texas Marine Science Institute
750 Channel View Dr.
Port Aransas, Texas 78373-5015

The statement of research interests should indicate how the proposed research activities would benefit from being based on the Gulf Coast and how the applicant might interact with existing research programs. Review of applications will start **January 15, 2007** and will continue until the position is filled. State law requires a background check on the selected applicant.

The University of Texas at Austin values diversity and is committed to Affirmative Action and Equal Opportunity. Women and minorities are encouraged to apply. UT Austin will make every effort to accommodate professional couples.

Hauptman-Woodward Medical Research Institute
Research Scientist
Protein Biochemistry

The Hauptman-Woodward Medical Research Institute is a private, not-for-profit organization studying the structures and functions of macromolecules of biomedical interest. The HWI is located in the Buffalo-Niagara Medical Campus, a consortium of research, clinical, and educational institutions founded to cultivate a world-class medical campus in downtown Buffalo. In the spring of 2005, HWI moved into a state-of-the-art new facility.

HWI Scientists have a long history in the determination of the structures of important biomolecules as well as the development of innovative methods that enable structure determination. To complement this structural expertise, we are recruiting in the area of protein biochemistry. Scientists who are studying macromolecular function through biochemical and biophysical techniques such as mass spectrometry, proteomics, spectroscopy, enzymology, and protein engineering are encouraged to apply. The independent Research Scientist will establish an active, extramurally funded research program.

A Ph.D. or M.D. in Biochemistry, Chemistry, or related areas as well as postdoctoral research experience are required. The new HWI Research Scientist will be hired at the equivalent of the Assistant, Associate, or Full Professor based on his or her qualifications. HWI Scientists receive appointments as faculty within the Department of Structural Biology at the State University of New York at Buffalo. For more information about current research programs and the new facility, visit our web site **http://www.hwi.buffalo.edu**. Interested applicants should submit a cover letter, curriculum vitae, research plan, and three letters of reference to: **George T. DeTitta, Ph.D., Hauptman-Woodward Medical Research Institute, 700 Ellicott St., Buffalo, NY 14203-1102;** email: **recruitment@hwi.buffalo.edu**. To ensure full consideration, application materials should be received by **January 15, 2007**.

The Hauptman-Woodward Institute is an Equal Opportunity Employer.

Max Planck Institute
for Demographic Research

Directors:
Prof. James W. Vaupel
Prof. Jan M. Hoem

The Max Planck Institute for Demographic Research is seeking to expand further its activities in the field of

Evolutionary Biodemography

by making a number of appointments at the levels of PhD (doctoral stipend) and Post-Doc (postdoctoral stipend) or Junior Research Scientist (TVöD 13).

The successful candidates will join a team of 20 scientists and research support staff who are striving to understand the evolutionary processes shaping patterns of aging and lifespan through integrated studies of age-specific death rates, fertility rates, growth and parental investment. The group aims to gain new insights through interdisciplinary research and in particular through the use of evolutionary approaches to understand age-specific demography. The research combines theoretical modeling with the analysis of existing databases and the execution of field and laboratory studies on various model species. The institute is seeking able scientists with strong track records who can contribute to this work in new and original ways. Applications from diverse backgrounds will be considered. Researchers with strong quantitative skills and either (1) grounding in evolutionary biology and an interest in learning demography or (2) grounding in demography and an interest in learning evolutionary biology, are particularly encouraged to apply, as are researchers with grounding in mathematical modeling and optimization who are interested in learning evolutionary biology and demography.

Applications should include a CV with a statement of academic interests and relevant experience, details of all qualifications including grades, a list of publications, the contact details of 3 referees. They should be sent by e-mail (biodemography-recruitment@demogr.mpg.de) to Prof. James W. Vaupel, Executive Director.

Review of applications will commence 15th January 2007 and continue until the positions are filled. PhD positions will typically commence September 2007 and other positions will commence as soon as possible after appointment.

Please see **www.demogr.mpg.de** for more information.

The Max Planck Society wishes to increase the share of women in areas where they are underrepresented, and strongly encourages women to apply.

The Max Planck Society is committed to employing more handcapped individuals and especially encourages them to apply.

Experimental Neuropathologist
The Department of Pathology
University of California, San Francisco

The Department of Pathology at the University of California, San Francisco, is seeking outstanding candidates for a tenure track position in experimental neuropathology, specifically in the areas of degenerative diseases of the nervous system. The successful applicant will be provided a start-up package and space to establish a strong independent research program and will be a member of the Biomedical Sciences Program. The applicant is expected to participate in teaching residents, fellows, and graduate and medical students. Applicants must have the MD or MD/PhD degrees, be eligible for California medical licensure and be Board certified or eligible in Anatomic Pathology and Neuropathology. Salary and appointment rank will be commensurate with the applicant's experience and training.

Applicants should send curriculum vitae, a brief statement of research plans and contact information for three letters of recommendation by **January 31, 2007** to:

Chair of Search Committee #M2860
C/O Shirley McFaden, Personnel Manager
UCSF Department of Pathology at Mount Zion
1600 Divisadero Street, Campus Box 0506
San Francisco, CA 94143-0506

UCSF is an Affirmative Action/Equal Opportunity Employer. The University undertakes affirmative action to assure equal employment opportunity for underutilized minorities and women, for persons with disabilities, and for Vietnam-era veterans and special disable veterans. UCSF seeks candidates whose experience, teaching, research, or community service has prepared them to contribute to our commitment to diversity and excellence.

NICHOLAS SCHOOL OF THE ENVIRONMENT AND EARTH SCIENCES
DUKE UNIVERSITY

Position in Earth System Analysis in Earth and Ocean Sciences (EOS)

Duke University's Division of Earth and Ocean Sciences in the Nicholas School of the Environment and Earth Sciences (NSEES) anticipates hiring a global hydrologist whose research emphasis is on climate change and water resources. We seek a natural scientist engaged in the interdisciplinary field of global hydrology, with a focus on the global water cycle, biogeochemical or geochemical properties of water resources, and/or human impacts from changes in global water systems. We seek a candidate with the ability to work at regional or global scales, using global earth systems models; advanced remote sensing technologies; and/or terrestrial observations of the amount and quality of surface and ground water. The candidate will be expected to work with Duke faculty to enhance existing scientific programs on climate change, water resources and hydrology. Additionally, the successful candidate may choose to work with researchers at the Nicholas Institute on Environmental Policy Solutions to establish an interface between climate change, changes in water cycling and quality and water policy.

The appointment is open at an assistant professor level. Candidates should possess a portfolio of experience and accomplishments, a strong interest in teaching and mentoring students, and the capacity for playing an active role in the School's water and climate change programs. The Nicholas School includes 50 faculty representing a diversity of disciplines. We offer professional and graduate degrees, and we direct Duke's undergraduate environmental programs.

Letters of interest should include a curriculum vitae and names of three references, and be sent to: **Chair, Earth System Analysis Search Committee, Division of Earth and Ocean Sciences, Nicholas School of the Environment and Earth Sciences, Box 90227, Duke University, Durham, NC 27708**. Applications are due by **January 1, 2006**.

Duke University is an Equal-Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

THE CHINESE UNIVERSITY OF HONG KONG

Applications are invited for:

Department of Biology / Department of Mathematics / Department of Computer Science & Engineering

Professor(s) / Associate Professor(s) / Assistant Professor(s)

(Ref. 06/215(147)/2)

The Chinese University of Hong Kong invites applications for three new faculty positions in bioinformatics and computational biology. Appointments will be made at Assistant Professor, Associate Professor or Professor levels as appropriate.

Applicants should have (i) a PhD degree in a relevant discipline, with preferably at least one year's postdoctoral experience; and (ii) strong commitment to excellence in teaching at the undergraduate and postgraduate levels. Those with longer years of relevant experience may be considered for appointment at a higher level. The appointees will work closely with the current CUHK team towards the formation of the centre/programme of bioinformatics and bio-technologies. Each appointee will become a member of one of the Departments of Biology, Mathematics, or Computer Science & Engineering according to his/her area of expertise, and will join various campus-based centres that connect theoretical and experimental researchers in bioinformatics from different departments in the biological, physical, mathematical and medical sciences, and engineering. Duties include (a) developing state-of-the-art research on integrative data analysis and interpretation using mathematical and statistical models for biological systems; (b) initiating and strengthening multidisciplinary collaboration addressing fundamental biological questions in model and non-model organisms; (c) conducting research with primary emphasis covering bioinformatics application of database, data mining, machine learning and algorithms; network modeling and systems biology; comparative genomics; or computational chemical genomics and structural bioinformatics and so on; (d) establishing and maintaining a vigorous, innovative and collaborative research programme; (e) participating in the teaching of departmental and interdepartmental postgraduate programmes; and (f) developing and delivering courses in bioinformatics for students in related departments. Appointments will initially be made on contract basis for up to three years, leading to longer-term appointment or substantiation later subject to demonstrated performance and mutual agreement. Review of applications will begin in late December 2006 and applications will be accepted until the posts are filled.

Salary and Fringe Benefits
Salary will be highly competitive, commensurate with qualifications and experience. The University offers a comprehensive fringe benefit package, including medical care, plus a contract-end gratuity for appointments of two years or longer and housing benefits for eligible appointees.

Further information about the University and the general terms of service for appointments is available at *http://www.cuhk.edu.hk/personnel*. The terms mentioned herein are for reference only and are subject to revision by the University.

Application Procedure
Please send a cover letter, full resume, copies of academic credentials, a publication list and/or abstracts of selected published papers, a research statement and a teaching statement (in pdf format) together with names, addresses and fax numbers/e-mail addresses of at least three referees to whom applicants' consent has been given for their providing references (unless otherwise specified), to *bio_recruit@cuhk.edu.hk*. The Personal Information Collection Statement will be provided upon request. Please quote the reference number and mark "Application - Confidential" on cover.

NICHOLAS SCHOOL OF THE ENVIRONMENT AND EARTH SCIENCES
DUKE UNIVERSITY

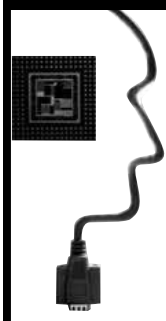
The Division of Earth and Ocean Sciences in Duke University's Nicholas School of the Environment and Earth Sciences (NSEES) anticipates hiring the second of two Jeffrey and Martha Gendell Chairs in Energy and the Environment. We seek a physical scientist who is a recognized authority on current and future energy resources. This individual's expertise would ideally encompass the availability of energy resources, the technologies and additional resources needed to extract, process, distribute and generate power from them, and the environmental impacts of the resource use. An understanding of the current and future demand for energy resources within the evolving geopolitical landscape of the world is highly desirable. So too are new ideas on the efficient utilization of energy resources. We are equally interested in candidates with a commitment to, and proven record of, interdisciplinary collaboration on problems at the intersection of energy with climate and water.

The appointment is open to all levels: assistant, associate and full professor. Candidates should possess a portfolio of experience and accomplishments commensurate with rank, a strong interest in teaching and mentoring students, and the capacity for playing an active role in the School's Energy and Environment Program. This role will include participating in collaborative initiatives between NSEES and other Duke Schools (Pratt School of Engineering, Fuqua School of Business, the Law School, the Terry Sanford Institute for Public Policy, and Trinity College) which are developing a broad, interdisciplinary program that addresses society's need for affordable, sustainable, safe and clean energy.

The Nicholas School includes 50 faculty representing a divesity of disciplines. We offer professional and graduate degrees, and we direct Duke's undergraduate environmental programs.

Letters of interest should include a curriculum vitae and names of three references, and be sent to: **Chair, Gendell Professorship Search Committee, Earth and Ocean Sciences, Nicholas School of the Environment and Earth Sciences, Box 90227, Duke University, Durham, NC 27708**. Applications are due by **January 1, 2005**.

Duke University is an Equal-Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.



Division Leader

The Theoretical (T) Division at Los Alamos National Laboratory is a multidisciplinary organization with a distinguished history, including 175 permanent Ph.D. scientists, an annual budget of over $80M, and the Center for Nonlinear Studies. Members conduct basic and applied research in theoretical physics, chemistry, biology, and mathematics. The Division carries out theoretical and computational research in support of the nation and Laboratory programs in weapons physics, basic science, materials science, threat reduction, and energy. Division Leader responsibilities include scientific leadership, recruitment and retention of staff, prudent fiscal management, infrastructure management, long-term planning, program development, project delivery, effective interaction with laboratory programs, and communication with sponsors and partners.

Required: Record of leading large, innovative technical organizations for simultaneous excellence in fundamental science and applied research. Major accomplishment in a relevant scientific discipline as demonstrated by a record of outstanding publications and international stature. Success in scientific management including effective resource management, teaming, conflict resolution, advocacy, negotiation skills, and strategic planning. Record of promoting scientific excellence by attracting and retaining outstanding research staff. Excellent communication skills. Commitment to institutional goals in the areas of health, safety and environmental protection, safeguards and security management, workforce diversity, and employee development. Ph.D. in relevant technical field of physical science. Ability to obtain a DOE Q clearance, which usually requires U.S. citizenship.

Desired: Knowledge of Laboratory, DOE, and other national programs. Experience in developing collaborations among national laboratories, universities, and industry. Record of fostering new scientific programs, developing new initiatives, and promoting cross-disciplinary research activities outside his/her own specialty.

To Apply: Send a comprehensive cover letter and CV/resume to **jobs@lanl.gov** referencing Job# 213775 in the subject line. AA/EOE

Los Alamos
NATIONAL LABORATORY

www.lanl.gov/jobs

UNC
N.C. CANCER HOSPITAL
LINEBERGER COMPREHENSIVE CANCER CENTER

Faculty Positions in Immunology

The UNC Lineberger Comprehensive Cancer Center and the Department of Microbiology and Immunology are searching for individuals with promising or established research programs in the broad areas of immunology. Candidates should have a Ph.D. and/or M.D. with a strong record of recent accomplishments as a postdoctoral fellow or sustained productivity as an established faculty member. Candidates chosen will be placed in tenure-track positions at The University of North Carolina at Chapel Hill. The search will be coordinated by Jenny Ting, Ph.D., Alumni Distinguished Professor and Immunology Program Leader, Lineberger Comprehensive Cancer Center.

Areas of interest include but are not limited to: Cancer immunology, immunity and infection, inflammation and cancer, innate immunity, macrophage and dendritic cell biology, immune signaling, and molecular immunology. Applicants should send a curriculum vitae, a description of research plans, and three letters of reference to:

Melissa Stroud Mack
UNC Lineberger Comprehensive Cancer Center, CB# 7295
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-7295

The University of North Carolina at Chapel Hill is an equal opportunity/ADA employer.
Women and minorities are encouraged to apply.

UNIVERSITY OF AARHUS, DENMARK

Professor in Nano-Foodscience

INTERDISCIPLINARY NANOSCIENCE CENTER

Applications are invited for a permanent position as professor in Nano-Foodscience at Interdisciplinary Nanoscience Center, University of Aarhus, Denmark.

The position is open as soon as possible.

Before applying for this position, please read the full job description at http://nat.au.dk/stilling. The deadline for receipt of all applications is
January 5, 2007, at 12.00 noon.
Please number the application 211/5-25

GRADUATE PROGRAM

UNIVERSITE PIERRE & MARIE CURIE — ENS — UCL

DUAL MASTERS IN "BRAIN AND MIND SCIENCES"

Université Pierre et Marie Curie in partnership with the Ecole Normale Supérieure and University College London

This 2-year international Masters level programme in Brain and Mind Sciences is offered by three of Europe's most prestigious centres of research and teaching in cognitive studies and neuroscience.

Applications for places for the 2007-2009 session are invited from outstanding students with applications from countries outside the European Union equally welcomed.

The programme will include a year spent in LONDON and a year in PARIS. Students will graduate with a Masters from UCL, a Masters level university diploma from UPMC/ENS and a DUAL MASTERS DEGREE IN BRAIN AND MIND SCIENCES awarded by the three institutions in partnership.

Students will be rigorously selected on the basis of academic excellence and academic recommendation. A maximum of 20 students will be accepted per academic year, 10 starting in PARIS and 10 in LONDON with cross-over after a year. Fees will be payable. For further information please contact one of academic course directors below. Scholarships may be available.

The programme is designed to give students a personalized programme of study in neuroscience and cognitive studies relevant to the Brain and Mind Sciences, through lectures and research projects conducted in both cities. Students will be able to re-orient, to apply different disciplines/competencies already acquired in pre-Masters study (eg engineering, mathematics, genetics), to study basic and clinical neuroscience or cognitive science topics in depth or broadly. The overarching educational aim is to give a grounding in Brain and Mind Sciences from a multi-disciplinary perspective and to provide a sound basis for choosing an appropriate topic and supervisor for doctoral research.

The course is designed to cater for students' individual interests and needs by access to major themes through existing established Masters programmes from which their curricula will be constructed:

- **Theme A:** Neuroscience - from molecules to systems (UPMC, ENS and UCL)
- **Theme B:** Clinical neuroscience (UCL)
- **Theme C:** Language, linguistics and semantics (ENS & UCL)
- **Theme D:** Cognitive psychology and neuropsychology (UCL)
- **Theme E:** Cognitive neuroscience (ENS and UPMC)
- **Theme F:** Biology of neurons (ENS)
- **Theme G:** Philosophy of sensation, emotion, action; philosophy of mind (ENS and UCL)

Depending on choice of modules students can aim to obtain:
(1) A theoretical grounding in neurobiological and cognitive research including philosophy of science, methods (including imaging, psychophysics and neuropsychology), molecular, cellular, genetic and integrative neuroscience.
(2) An appreciation of the way Brain and Mind questions can be approached theoretically and experimentally in humans and other model systems.
(3) An appreciation of the interaction between theory, modelling and empiricism in tackling Brain and Mind problems
(4) Practical experience of investigating Brain and Mind problems from two cultural and historical perspectives (in the two cities).

Students should be prepared to follow lectures in English and French. Language classes will be available in both cities. Examinations and dissertations may be written in English in both cities.

For further information consult **http://www.ion.ucl.ac.uk/education/msc-brain-mind.htm** and/or **http://diu-neuro.snv.jussieu.fr**.

Applications in either English or French should be sent to either:

- **Dr. Caroline Selai, Institute of Neurology, Queen Square, London WC1N 3BG, UK (c.selai@ion.ucl.ac.uk)**, or
- **Dr. Ann Lohof, Laboratoire DVSN, UMR 7102, Case 14, Université P et M Curie, 9 quai St Bernard, 75005 Paris (Ann. Lohof@mail.snv.jussieu.fr)**, or
- **Dr. Andrea Dumoulin, Laboratoire de Biologie Cellulaire de la Synapse, Inserm U497, Ecole Normale Supérieure 46, rue d'Ulm, 75005 Paris (adumoul@biologie.ens.fr)**

in the form of a curriculum vitae with achieved or expected examination scores, a personal statement/letter of motivation of not more than 1 A4 page, and the names and email addresses of 2 academic referees.

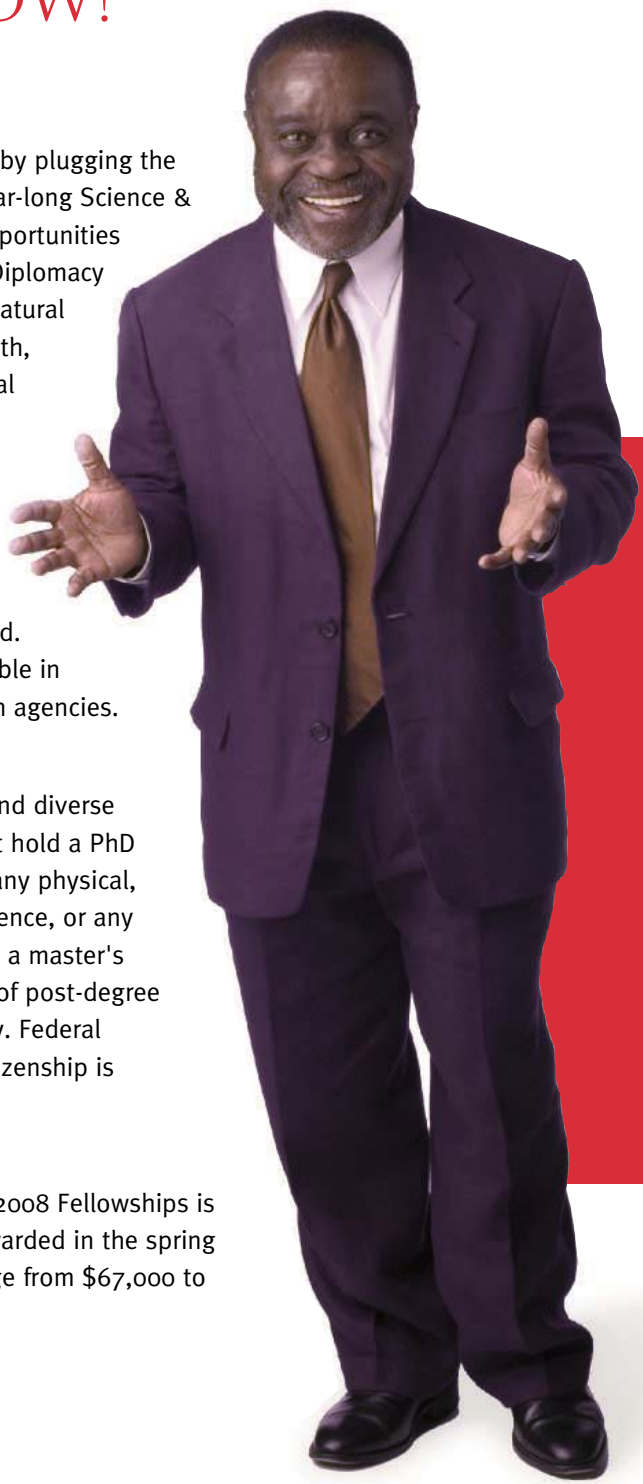
PICTURE YOURSELF AS A AAAS SCIENCE & TECHNOLOGY POLICY FELLOW!

Advance your career and serve society by plugging the power of science into public policy. Year-long Science & Technology Policy Fellowships offer opportunities in six thematic areas: Congressional • Diplomacy • Energy, Environment, Agriculture & Natural Resources • Global Stewardship • Health, Education, & Human Services • National Defense & Global Security.

Work in Dynamic Washington, D.C.
Since 1973, AAAS Fellows have been applying their expertise to federal decision-making processes that affect people in the U.S. and around the world. A broad range of assignments is available in the U.S. Congress and executive branch agencies.

Join a Network of Nearly 2,000 Fellows.
AAAS Fellows benefit from a growing and diverse network of colleagues. Applicants must hold a PhD or equivalent doctoral-level degree in any physical, biological, medical/health, or social science, or any engineering discipline. Individuals with a master's degree in engineering and three years of post-degree professional experience also may apply. Federal employees are not eligible and U.S. citizenship is required.

Apply Now!
The application deadline for the 2007-2008 Fellowships is 20 December 2006. Fellowships are awarded in the spring and begin in September. Stipends range from $67,000 to $87,000, depending on experience.
To apply: fellowships.aaas.org



Enhancing Public Policy, Advancing Science Careers

Fred Boadu, JD, PhD

Agricultural Economics, University of Kentucky.

2005-2006 AAAS Fellow at the U.S. Department of Agriculture, Food Safety Inspection Service, Office of Policy, Program and Employee Development. Also a 1993-1994 AAAS Fellow at the U.S. Agency for International Development, Bureau for Africa/Bureau for East Asian and Pacific Affairs.

Currently associate professor and assistant head of department for undergraduate programs at Texas A & M University, which granted him a faculty development leave to complete the 2005-2006 AAAS Fellowship.

AAAS
ADVANCING SCIENCE, SERVING SOCIETY

EMINENT SCHOLAR IN BIOENERGY

The University of Georgia and the Georgia Research Alliance (GRA) invite applications from accomplished scientists for an endowed chair in the field of bioenergy research. This newly established position has been created as an important component of the State of Georgia's new bioenergy initiative. The position builds on the University's strengths in plant genetics, glycobiology, structural biology, microbiology, and forest biotechnology. Applications are encouraged from established and successful research scientists who have outstanding records of scholarship, extramural funding and program building in areas relevant to bioenergy research. These may include but are not limited to cellulosic biomass structure and processing, enzyme-substrate (cellulose) interactions, biomass crop modification, systems biology of biomass conversion, and biofuel production. The University of Georgia provides a highly interdisciplinary and supportive environment conducive to the development of innovative collaborations. This tenured position comes with an endowment commensurate with this prestigious opportunity. College and departmental affiliations will be based on the candidate's credentials and interest.

Review of applications will begin on **January 30, 2007**. Applications received by that date are assured full consideration. Please email a statement of interest, CV, research and teaching statements and the names of three references (all in PDF format) to **adams@bmb.uga.edu**.

Letters of recommendation should be mailed to: **Professor Michael W. W. Adams, Chair, GRA Eminent Scholar in Bioenergy Search Committee, Department of Biochemistry and Molecular Biology, Fred C. Davison Life Sciences Building, University of Georgia, Athens, GA 30602.**

The University of Georgia is an Affirmative Action/Equal Opportunity Employer.

The University of Georgia

USF HEALTH UNIVERSITY OF SOUTH FLORIDA — Silver child DEVELOPMENT CENTER

http://hsc.usf.edu · 12901 Bruce B. Downs Blvd, MDC 02 · Tampa, FL 33612

Robert A. Silver Chair in Developmental Neurobiology

Department of Psychiatry and Behavioral Medicine College of Medicine, University of South Florida Health

The Department of Psychiatry and Behavioral Medicine, College of Medicine, USF Health, in partnership with the Silver Child Development Center, seeks an outstanding scientist for the position of Robert A. Silver Chair in Developmental Neurobiology. The successful candidate is expected to have an established academic and professional focus in behavioral neurosciences and neurodevelopmental disorders in infants and children.

The Silver Child Development Center is an interdisciplinary research environment that focuses on research on typical and atypical brain development and function. Its 15 scientists and clinicians collaborate to understand the biological and environmental factors responsible for disorders of thought, learning, communication and behaviors translating this knowledge into more effective therapeutic strategies. USF Health consists of the colleges of Medicine, Nursing, and Public Health. Also included are the schools of Basic Biomedical Sciences and Physical Therapy. In partnership with its affiliated hospitals, USF Health's research funding last year was $134 million - more than half of which came from federal sources. USF is one of only 95 public and private universities in the U.S. that have been designated as Carnegie Comprehensive Doctoral Research University/Very High Research Activity.

Minimum requirements include a MD, Ph.D., or MD/Ph.D. with a minimum of five years of experience as an Associate Professor or equivalent. A record of sustained accomplishments and evidence of leadership in his/her field, relevant administrative experience, and evidence of effective interpersonal, collaborative, and communication skills is required. The successful candidate is expected to have a distinguished record of scholarly activity, continuous NIH R01 and other extramural funding and requisite teaching experience in a medical/graduate curriculum. A legacy of building interdisciplinary programs and experience with successfully mentoring graduate and medical students, postdoctoral-fellows, and junior faculty is also required.

Applicants should submit, by email, a letter summarizing their qualifications and interests in the position, future research plans, curriculum vitae and the names and contact information of five references. Completed applications must be submitted to: **Ms. Vanessa Ayer (vayer@health.usf.edu)**. Competitive start-up packages and salaries will be provided commensurate with experience. Review of applications will begin November 1, 2006 and will continue until this position is filled. For more information please visit this website **http://hsc.usf.edu/medicine/silver_chair_announcement.html.**

*USF Health is committed to increasing its diversity and will give individual consideration to qualified applicants for this position with experience in ethnically diverse settings, who possess varied language skills, or who have a record of research issues that support/benefit diverse communities or teaching a diverse student population. The University of South Florida is an Equal Opportunity/Affirmative Action/Equal Access Institution. For disability accommodations, contact **Vanessa Ayer** at **813-974-8349** within 5 days of an event. According to Florida law, search records, including applications and search committee meetings, are open to the public.*

50 YEARS

ILLINOIS
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Director Micro and Nanotechnology Laboratory

The Micro and Nanotechnology Laboratory (MNTL) is a state-of-the-art multidisciplinary research facility in the College of Engineering at the University of Illinois at Urbana-Champaign. The laboratory currently contains 72,000 net square feet of office and laboratory space, including 8,000 net square feet of Class 100 and Class 1000 clean rooms. In January 2007, a $20 million expansion of the building will be complete, providing an additional 45,000 square feet of laboratory and office space. Included in the new laboratory space are 3,000 square feet specifically designed for bionanotechnology.

Faculty and students affiliated with the laboratory conduct research in photonics, microelectronics, nano- and microelectromechanical systems (NEMS, MEMS), and biotechnology. The University of Illinois is a world leader in research in these areas.

The MNTL includes special facilities for (1) the growth of artificially structured semiconductor materials, including Molecular Beam Epitaxy (MBE), Chemical Beam Epitaxy (CBE), and Metal-Organic Chemical Vapor Deposition (MOCVD), (2) the fabrication of nanometer scale silicon and compound semiconductor electronic and optoelectronic devices, such as MOSFETs, MESFETs, HBTs, MEMS/NEMS, semiconductor lasers, waveguides, and modulators, utilizing electron beam and optical lithography, plasma-enhanced deposition of oxides and nitrides, sputter deposition, thermal and electron-beam metallization, and reactive ion etching, (3) ultrahigh-speed optical and electrical measurements; and characterization of semiconductor materials, and (4) fluorescence microscopy to study cell-device interactions. Faculty members and students also have access to extensive computing resources.

The Director of the MNTL reports to the Dean of the College of Engineering and will provide overall leadership and direction of the Laboratory and its research programs. The Director formulates strategic plans, prepares and implements the annual budget, oversees the administrative affairs of the Laboratory, and serves as the principal spokesperson for the Laboratory. An important challenge for the new director will be to provide the leadership and long-term vision to leverage the capabilities of the MNTL with the broad expertise in electronic, optical, MEMS/NEMS, materials, devices, bio, circuits and systems which exists on the campus as well as outside the campus. The Director oversees the various research facilities in the Laboratory, and, in cooperation with the faculty affiliated with the MNTL, solicits partnerships and funding from industry and government.

Candidates must have an earned doctorate or comparable academic credentials in a science or engineering field, a proven record of science or engineering research, and a substantial record of acquiring support for research and administering research programs. Candidates should be qualified for an appointment as tenured professor in one of the departments of the College of Engineering, and must show evidence of strong entrepreneurial, administrative, and communication skills.

In order to receive full consideration, applicants must respond by **February 15, 2007**. This is a full-time position. The starting date is negotiable, and could begin as early as August, 2007. Salary is commensurate with experience. Applications, including the names and address of at least three references, should be sent to:

Search Committee for MNTL Director
c/o Kathy Darr
306 Engineering Hall
1308 West Green Street
Urbana, IL 61801
e-mail: kdarr@uiuc.edu

The University of Illinois at Urbana-Champaign is an Affirmative Action/Equal Opportunity Employer.

POSITIONS OPEN

Sidwell
FRIENDS SCHOOL

SCIENCE DEPARTMENT CHAIR
Sidwell Friends School

Sidwell Friends, a coeducational Quaker day school in Washington, D.C., seeks seasoned Educator to serve as Chair of its Science Department (grades five to 12). The Chair is responsible for maintaining and enriching the School's Science Program and, with the Middle and Upper School Principals, evaluates science faculty and curriculum. Master's or Ph.D. in an appropriate discipline, seven or more years of classroom teaching, administrative experience in leading a challenging and cutting-edge science program, and the ability to communicate clearly and effectively with diverse constituencies are required. This ten-month position begins August 2007. Send cover letter, resume, and names of three references to: **Human Resources, Sidwell Friends School, 3825 Wisconsin Avenue N.W., Washington, DC 20016; fax: 202-537-2418; website: http://www.sidwell.edu; e-mail: hr@sidwell.edu.** *Equal Opportunity Employer.*

NEW DIRECTOR SOUGHT FOR THE NASA Institute for Advanced Concepts (NIAC)

The Universities Space Research Association (USRA), a private, nonprofit consortium of 100 Colleges and Universities, is seeking a Director for its NASA Institute for Advanced Concepts (NIAC). NIAC, which is located in Atlanta, Georgia, provides an independent, open forum for the external analysis and definition of space and aeronautics advanced concepts to complement the advanced concepts activities conducted within NASA. Through a competitive process, NIAC selects and funds Fellows to develop revolutionary concepts, specifically systems and architectures, that can have a major impact on NASA missions in the time frame of 10 to 40 years in the future.

The NIAC Director provides management oversight of all aspects of the Institute's operations and serves as an advocate for its programs within NASA, other government agencies, and the University community. The Director must be able, therefore, to encourage within Fellows and prospective Fellows of NIAC a creative but credible imagination across a broad spectrum of scientific disciplines. The Director must be able, as well, to provide articulate leadership to persuade NASA and other aerospace government agencies to invest in high-risk, high-payoff concepts that could have a significant impact on future missions.

The applicant should possess a Ph.D. in a technically relevant field, have a broad research background with at least 10 years of experience in managing research efforts in an entrepreneurial environment, be familiar with NASA, and be eligible for a security clearance. Salary and benefits are competitive and commensurate with experience. USRA offers an excellent comprehensive fringe benefits program. Interested individuals should submit a letter of intent and curriculum vitae along with the names and contact information for three references to **e-mail: niacsearch@hq.usra.edu.** Applications received by January 30, 2007, will be given full consideration. Further information regarding the NIAC and USRA may be found at **websites: http://www.niac.usra.edu** and **http://www.usra.edu,** respectively.

Dr. Hussein Jirdeh, Search Coordinator, Universities Space Research Association, 10211 Wincopin Circle, Suite 500 Columbia, MD 21044. *USRA is an Equal Opportunity Employer.*

MONTANA STATE UNIVERSITY. Tenure-track **ASSISTANT PROFESSOR** of plant genetics, nine-month academic year appointment. Candidates must have a Ph.D. in plant genetics, plant pathology, plant sciences, or related field. Complete position announcement and application procedure may be seen at **website: http://www.montana.edu/level2/jobs.html.** Screening begins February 1, 2007, start date is August 15, 2007. *ADA/Equal Opportunity Employer/Affirmative Action, Veterans Preference.*

POSITIONS OPEN

FACULTY POSITION
Bio-Nano Marshall University

As part of a statewide initiative in nanotechnology, the College of Science at Marshall University (MU) invites outstanding **MOLECULAR and CELL SCIENTISTS** with research interests at the bio-nano interface, broadly defined, to apply for a tenure-track position at the **ASSISTANT or ASSOCIATE PROFESSOR** level. Priority will be given to those who can contribute to Marshall's interdisciplinary cell differentiation and development research program. He/she will work in a new, state-of-the-art facility **(website: http://windowsmedia.marshall.edu/rcbbiotechvid.wmv)** with basic scientists from both the College of Science and the School of Medicine and collaborate in an inter-institutional molecular recognition and transport project with scientists and engineers at West Virginia University. Excellence in research and teaching at the graduate and undergraduate levels is expected. Applicants must hold a Ph.D. in biology or chemistry or a related field and have relevant postdoctoral experience. To apply, send full curriculum vitae and summaries of research experience and future research plans to: **Michael Norton, Ph.D., Search Committee Chair, Department of Chemistry, Marshall University, One John Marshall Drive, Huntington, WV 25755.** Applicants should also arrange to have three letters of recommendation submitted on their behalf. Review of applications will begin December 30, 2006, and continue until the position is filled. *MU is an Affirmative Action/Equal Opportunity Institution.*

ASSISTANT PROFESSOR/ MICROBIOLOGIST/ ECOLOGIST
Department of Biology
Ball State University
Muncie, Indiana

Tenure-track position available August 17, 2007. Responsibilities: teaching undergraduate and graduate courses in microbiology for allied health sciences, general ecology, and aquatic microbiology; development of a research program involving undergraduate and graduate students and grant procurement; providing service to the academic community. Minimum qualifications: earned doctorate in a biological or environmental science by November 1, 2007, effective written and oral communication skills, commitment to excellence in teaching, and competency in current approaches in environmental microbiology. Preferred qualifications: demonstrated teaching ability and publications and/or evidence of other scholarly activity.

Send letter of application, curriculum vitae, documentation of scholarly activity and teaching ability (e.g., student and peer-review evaluation summaries), copies of transcripts, and three letters of reference to: **Dr. John McKillip, Chair, Microbiologist Search Committee, Department of Biology, Ball State University, Muncie, IN 47306.** Review of applications will begin immediately and will continue until the position is filled. **(Website: http://www.bsu.edu.)** *Ball State University is an Equal Opportunity, Affirmative Action Employer and is strongly and actively committed to diversity within its community.*

POSTDOCTORAL POSITION IN COMPUTATIONAL BIOLOGY
Institute of Computational Medicine
Johns Hopkins University, Baltimore, Maryland

We are looking for motivated researchers with a strong foundation in both life sciences and quantitative methods development and demonstrated programming skills to develop and implement mathematical models to predict the functional impact of somatic mutations in tumor tissues.

He/she will work in a highly collaborative environment at the Institute of Computational Biology in the Karchin laboratory, **website: http://karchinlab.org.**

Please e-mail cover letter, PDF of curriculum vitae, and names and e-mail addresses of three references to **Dr. Rachel Karchin, e-mail: karchin@jhu.edu.**

POSITIONS OPEN

West Virginia University
ROBERT C. BYRD HEALTH SCIENCES CENTER

A **RESEARCH SCHOLAR POSITION** is available in the School of Medicine at West Virginia University to study the cardiac ion channels. A Master's degree in biology-related field is required. Experience with basic molecular biology techniques such as reverse transcription polymerase chain reaction is essential, which should be supported by publications. This position will remain open until filled. Please send resume and three references to **Ms. Vickie White** at **e-mail: vwhite@hsc.wvu.edu.** *West Virginia University is an Affirmative Action/Equal Opportunity Employer.*

ASSISTANT OR ASSOCIATE PROFESSOR, BIOLOGY
Baruch College/City University of New York

The Department of Natural Sciences at Baruch College/City University of New York (CUNY) invites applications for a tenure-track position in biology at the **ASSISTANT OR ASSOCIATE PROFESSOR** rank. The Department seeks an **ENVIRONMENTAL BIOLOGIST** to teach introductory courses in environmental studies. Additionally, the candidate will collaborate with other faculty to develop new courses in environmental biology for science majors and for students preparing for careers in areas such as business, law, and public service. The candidate must establish a vigorous research program and mentor undergraduates in independent study and honors research.

Salary: Competitive and commensurate with qualifications and experience.

Ph.D. required for appointment as an Assistant or Associate Professor. The successful candidate must be committed to excellence in undergraduate teaching and research. Experience with teaching large lecture sections is desirable.

Please send curriculum vitae and three letters of recommendation by January 1, 2007, to:

Search Committee, Assistant/Associate Professor, Biology
Baruch College/The City University of New York
Attn: Professor John H. Wahlert, Chair
Department of Natural Sciences
One Bernard Baruch Way, Box A-0506
New York, NY 10010

An Affirmative Action/Equal Opportunity/Americans with Disabilities Act Employer.

FACULTY POSITION IN BIODEFENSE AND/OR MEDICAL MICROBIOLOGY

The Department of Pathology, Microbiology and Immunology, School of Medicine, University of South Carolina (USC), Columbia, is undergoing major expansion. Applications are invited for a tenure-track **ASSISTANT/ASSOCIATE/FULL PROFESSOR** position in biodefense and/or medical microbiology. Candidates at the Assistant Professor level must have a Ph.D. or M.D. or equivalent with postdoctoral research experience. Candidates at the Associate/Full Professor level should have current extramural funding. Competitive salary and startup funds are available. Candidates are expected to develop a strong, extramurally funded research program and participate in the teaching mission of the Department. Candidates should have interests in collaborating with existing faculty to develop interactive research projects: For further information see the departmental **website: http://pathmicro.med.sc.edu.** Apply with curriculum vitae, statement of research plans, and three references to: **Dr. Mitzi Nagarkatti, Chair, Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, SC 29208** or **e-mail: infectiousdiseases@gw.med.sc.edu.**

The search will start immediately and continue till the position is filled.

USC Columbia is an Equal Opportunity Affirmative Action Employer and encourages applications from women and minorities.

Charles H. Best Postdoctoral Fellowship

BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH

University of Toronto

Charles H. Best Postdoctoral Fellowships are awarded each year to highly qualified graduates (2 years or less postgraduate) in the field of molecular, genetic and genomic research. The two year fellowship is tenable in the Banting and Best Department of Medical Research at the University of Toronto. Individual research programs include studies on functional genomics, gene expression, signal transduction, development, membrane transport and protein structure.

Applications should be addressed to: **Dr. Henry Krause, Chair, C.H. Best Fellowship Committee, DCCBR, 160 College St., Toronto, Ontario, Canada, M5S 3E1**, and should include a curriculum vitae, transcripts and three letters of reference. Applicants are also strongly encouraged to contact one or two potential supervisors whose interests and e-mail addresses are posted on our Departmental WEB page (**http://www.utoronto.ca/bandb**).

The deadline for applications is **January 15, 2007**.

ST. THOMAS UNIVERSITY

"Developing Leaders For Life"

FACULTY – BIOLOGY

St. Thomas University invites applications for a continuing track position in biology at the Assistant, or Associate Professor level, depending on experience, starting August 2007. A PhD and three years postdoctoral laboratory research experience required. Applicants at the Associate level must have an established and funded research program.

We are searching for an individual who will thrive in a liberal arts environment that combines a strong commitment to teaching and research. Mentoring of undergraduate research students is expected. Candidates with research interests that complement the developing cell science program are particularly encouraged to apply. Specifically, research involving microbial physiology and developmental genetic models will be given preference. The successful candidates will be expected to teach at all levels of the curriculum and establish an externally funded research program that provides rigorous collaborative research projects for undergraduates. Opportunities exist for research collaboration within the developing biomedical research community spawned by the newly forming Scripps Research Institute in South Florida.

Research laboratory space and infrastructure will be provided in our new building. Lab facilities include molecular, histological and microscopy cores.

The department is a multi-discipline unit consisting of 20 full-time and adjunct faculty members. We offer Bachelor of Arts degrees in biology, computer science, and computer information systems in addition to our pre-nursing and pre-engineering programs.

Located in Miami Gardens, Florida, St. Thomas University is a Catholic university with rich cultural and international diversity. Our community includes more than 2600 students and 105 full-time faculty members. Further information is available at **http://www.stu.edu/**.

Completed applications received by **February 1, 2007** will receive full consideration with later applications as needed until position is filled. Send letter of application, curriculum vitae, undergraduate and graduate transcripts (unofficial copies are acceptable initially), statement of research interests, statement of teaching philosophy, and a list of at least three references to: **Lenore Prado, Associate Director of Human Resources, St. Thomas University, 16401 NW 37 Ave., Miami Gardens, FL 33054. Email: facsearch@stu.edu. Fax: (305) 628- 6510**.

St. Thomas University is an Equal Opportunity Employer.

THE UNIVERSITY OF TEXAS AT SAN ANTONIO ASSOCIATE or FULL PROFESSOR PROTEOMICS

The University of Texas at San Antonio (UTSA) is accepting applications for a tenured Associate Professor or Full Professor position, starting Fall 2007. The appointment will be in the broad area of proteomics.

The required qualifications are: an established program of research in proteomics, excellence in teaching, experience in directing doctoral dissertations, and a record of success in obtaining external funding.

Responsibilities include leadership in developing the new UTSA Proteomics Core Facility, teaching, supervising research students at all levels, and maintaining an externally funded research program. UTSA, the second largest component university of The University of Texas System, has an enrollment in excess of 28,000 students. The Biology Department has 47 tenured/tenure-track faculty members, approximately 3,000 undergraduate majors, 150 graduate students in two M.S. programs (Biology, Biotechnology), and 50 doctoral students in two Ph.D. programs (Neurobiology, Cell and Molecular Biology). The Department of Chemistry has 15 tenured/tenure-track faculty members, approximately 145 undergraduate majors, 12 graduate and 11 doctoral students.

Review of submitted applications will begin immediately and will continue until the position is filled. Applicants who are not U.S. citizens must state their current visa and residency status. Applicants must submit a letter of application, a dated current curriculum vitae, a description of current research and research plans, a statement of teaching philosophy, and the names, postal addresses, and e-mail addresses of three individuals who can provide recommendation letters. Application materials should be sent to: **Proteomics Search Committee, 1.620 BSE, The University of Texas at San Antonio, One UTSA Circle, San Antonio, Texas 78249-0661**, or electronically to **PROT@utsa.edu**. Applications will be treated as confidential. Budget approval for position is pending.

UTSA is an Affirmative Action/Equal Opportunity Employer. Women, minorities, veterans, and individuals with disabilities are encouraged to apply.

USF HEALTH UNIVERSITY OF SOUTH FLORIDA

http://hsc.usf.edu · 12901 Bruce B. Downs Blvd, MDC 02 · Tampa, FL 33612

Bob and Diane Roskamp Chair in Biological Psychiatry

Department of Psychiatry and Behavioral Medicine

College of Medicine, University of South Florida Health

The Department of Psychiatry and Behavioral Medicine, College of Medicine, USF Health, seeks an outstanding scientist for the position of Bob and Diane Roskamp Chair in Biological Psychiatry. The successful candidate is expected to have an established academic and professional focus in behavioral neurosciences. Their area of research interest may relate to neuroinflammation, genetic susceptibility, and the biological basis of the pathophysiology and treatment of psychotic illnesses inclusive of schizophrenia and mood disorders. The Department of Psychiatry and Behavioral Medicine currently has over 67 faculty and over $3 million annually in NIH and other external grants. USF is one of only 95 public and private universities in the U.S. that have been designated as Carnegie Comprehensive Doctoral Research University/Very High Research Activity.

Minimum requirements include a MD, Ph.D., or MD/Ph.D. with a minimum of five years of experience as an Associate Professor or equivalent. The successful candidate is expected to have a distinguished record of scholarly activity, continuous NIH R01 and other extramural funding and requisite teaching experience in a medical/graduate curriculum. A reputation for building interdisciplinary programs and experience with successfully mentoring graduate and medical students, postdoctoral-fellows, and junior faculty is also required.

Applicants should submit, by email, a letter summarizing their qualifications and interests in the position, professional goals, curriculum vitae and the names and contact information of five references. Completed applications must be submitted to **Ms. Vanessa Ayer (vayer@health.usf.edu)**. Competitive start-up packages and salaries will be provided commensurate with experience. Review of applications will begin December 1, 2006 and will continue until this position is filled. For more information, please visit this website: **http://hsc.usf.edu/medicine/roskamp_chair_announcement.html.**

*USF Health is committed to increasing its diversity and will give individual consideration to qualified applicants for this position with experience in ethnically diverse settings, who possess varied language skills, or who have a record of research issues that support/benefit diverse communities or teaching a diverse student population. The University of South Florida is an Equal Opportunity/Affirmative Action/Equal Access Institution. For disability accommodations, contact **Vanessa Ayer** at **813-974-8349** within 5 days of an event. According to Florida law, search records, including applications and search committee meetings, are open to the public.*

50 YEARS CELEBRATING SUCCESS

POSITIONS OPEN

ASSOCIATE DEAN FOR RESEARCH AND DEVELOPMENT
Website: http://www.cnsm.csulb.edu

The College of Natural Sciences and Mathematics at California State University, Long Beach (CSULB), seeks an Associate Dean for Research and Development starting fall 2007. The ideal candidate has strong involvement in public/private partnerships and research/grant collaborations across science, technology, engineering, and mathematics (STEM) disciplines; significant administrative and academic governance experience; experience with assessment and grant evaluation. Will facilitate faculty collaboration and promote interdisciplinary research and research centers. Promote and support student research and student organizations. Position is 0.75 time base as a 12-month Associate Dean at Administrator III level, and a 0.25 time base as an academic year tenured, full Professor. (Ph.D. required in one of the natural sciences, mathematics, or math/science education or closely related field to qualify applicant for retreat rights as full Professor with tenure to a department in the College.) Evidence of very strong publications, research, and grant acquisitions. Evidence of ability to work collaboratively with a diverse faculty and University staff.

For a more detailed job description visit **website: http://www.csulb.edu/aa/personnel/jobs,** recruitment number 149.

Review of applications to begin on February 1, 2007. Applicants should submit the following: letter of application addressing qualifications, curriculum vitae (include e-mail address), three letters of recommendation directly from referees, the names, addresses, telephone numbers of two additional professional references, and official Ph.D. transcript (required of finalists) to the **Search Committee** at: **Stephen Mezyk, Chair, Search Committee – Associate Dean for Research and Development, College of Natural Sciences and Mathematics, California State University, Long Beach, 1250 Bellflower Boulevard, Long Beach, CA 90840-4501. E-mail: jbright@csulb.edu; telephone: 562-985-1521; fax: 562-985-2315.**

CSULB is an Equal Opportunity Employer.

CHAIR OF BIOLOGICAL SCIENCES
Michigan Technological University

The Department of Biological Sciences at Michigan Technological University invites applications for the position of Chair to begin in the 2007-2008 academic year. The successful candidate will have a Ph.D. in the biological sciences or a related area, a distinguished record of research and teaching, evidence of leadership in procurement of extramural funding, and be eligible for appointment as **FULL PROFESSOR.** The Chair is expected to maintain a dynamic research program compatible with existing departmental strengths in biochemistry and molecular biology, ecology and limnology, and the health sciences.

We seek an individual with the vision and skills to lead the Department to national prominence in biological research, further our strong tradition of educational excellence, grow our M.S. and Ph.D. programs, and advance the Department's position as a key player in interdisciplinary strategic initiatives such as sustainability and biotechnology.

Review of applications will begin January 5, 2007, and continue until the position is filled. For a broader position description see **website: http://www.bio.mtu.edu/.** Applicants should send: a letter of interest; curriculum vitae; statements of research, teaching, and administrative philosophies; and names of four references to:

Dr. Casey Huckins, Search Committee Chair
Department of Biological Sciences
Michigan Technological University
1400 Townsend Drive
Houghton, MI 49931

Michigan Technological University is an Equal Opportunity Educational Institution/Equal Opportunity Employer/Affirmative Action Employer.

JOHN J. CRAIGHEAD ENDOWED CHAIR

The Division of Biological Sciences (DBS) at the University of Montana invites applications for an **ENDOWED CHAIR** (tenure-track) at the **ADVANCED ASSOCIATE PROFESSOR/FULL PROFESSOR** level, to begin August 2007. This position has been established to honor the distinguished career of **Dr. John J. Craighead** and to carry on his research interests in the study and conservation of large mammals in the wild. The position involves responsibilities in the Wildlife Biology Program (WBIO) and DBS. The successful candidate is expected to develop a vigorous externally funded research program in the ecology and conservation of large mammals, mentor M.S. and Ph.D. students in DBS and WBIO, teach a graduate level course in area of interest, and interact with state, federal, and private conservation organizations. Requirements include a Ph.D., demonstrated international recognition of research achievement in the area of large mammal ecology and conservation in the wild consistent with Dr. Craighead's legacy, demonstrated success in securing grant funding, demonstration of a potential for or a record of teaching excellence, and a proven ability to communicate effectively with professionals and the general public. Preference will be given to applicants whose research profile includes carnivore ecology, international experience, and those who possess experience directing graduate student research. Send a one to two-page summary of research interests and plans, curriculum vitae and names of at least three references to: **Dr. Kerry R. Foresman, Search Committee Chair, HS104, Division of Biological Sciences, The University of Montana, Missoula, MT 59812 U.S.A. Telephone: 406-243-4492.** Inquiries may be made by e-mail **(e-mail: foresman@mso.umt.edu)** but no faxed or e-mail applications will be accepted. A detailed position description is available on the DBS **website: http://biology.dbs.umt.edu/dbs.** Review of applications begins 15 January 2007. *Affirmative Action/Equal Opportunity Employer.*

ASSISTANT DEAN FOR GRADUATE EDUCATION

The School of Medicine at the University of North Carolina at Chapel Hill is searching for an Assistant Dean for Graduate Education (ADGE). The ADGE will create, develop, and administer a new umbrella graduate admissions program for students entering Ph.D. programs in the biological and biomedical sciences, in both the School of Medicine and the College of Arts and Sciences. The successful candidate will supervise a staff that will work closely and effectively with the graduate directors of 13 Ph.D. granting programs and campuswide curricula. ADGE applicants should hold a Ph.D. or M.D. in a biological or biomedical discipline, have substantial research experience, and demonstrate a strong leadership record in innovative training of graduate students. The ADGE will be vested with a tenured faculty position in an appropriate academic department (rank to be determined) and will be expected to either maintain an active research program or participate in departmental teaching responsibilities. Applicants should send curriculum vitae, names of three reerences, and a brief statement of relevant experience to:

ADGE Search Committee
Office of Research, School of Medicine
CB-7000, 43 MacNider
University of North Carolina
Chapel Hill, NC 27599-7000

Review of applications will commence December 1, 2006.

POSTDOCTORAL POSITION to study molecular and cellular mechanisms of angiogenesis, with particular emphasis on neovascular eye diseases such as diabetic retinopathy. Prior background in molecular and/or cell biology would be helpful, but is not essential. Send curriculum vitae and names of three references to: **Dr. E. Duh, Johns Hopkins University School of Medicine, 1550 Orleans Street, Room 143, Baltimore, MD 21231. E-mail: eduh@jhmi.edu.** *Equal Opportunity Employer.*

NEW FACULTY POSITIONS
Department of Pharmacology, Toxicology, and Therapeutics
University of Kansas Medical Center (KUMC)

The Department of Pharmacology, Toxicology, and Therapeutics under the direction of **Curtis Klaassen, Professor and Chair (website: http://www.kumc.edu/pharmacology/),** is continuing its expansion by inviting applications for two **ASSISTANT PROFESSORS,** tenure-track faculty positions to augment the strength of our eight recent hires. Preference will be given to candidates in areas such as nuclear receptors, toxicology, or xenobiotic disposition (absorption, distribution, metabolism, excretion) that complement existing strengths in the Department and the Medical Center. This expansion is supported by a new Centers of Biomedical Research Excellence (COBRE) grant entitled Nuclear Receptors in Liver Function and Dysfunction, a recently renewed training grant in environmental sciences, and a new research building. Broad areas of strength at the Medical Center include cancer, neuroscience, reproductive biology, renal pathophysiology, and growing efforts in liver biology. A competitive startup package and appropriate space will be offered. Standard support facilities are present, including biotechnology, transgenics, proteomics, and a state-of-the-art imaging center. The Department also has excellent molecular biology (robot, real time PCR, sequencer), and liquid chromatography/mass spectrometry facilities. Applications will be reviewed as they are received until the positions are filled. Anticipated appointment date is as early as July 1, 2007. Applicants must be proficient in the use of the English language. Applicants should provide curriculum vitae, statement of research interests, and names of three references. To review the position description and apply online go to **website: http://jobs.kumc.edu** and search for position J0020073. Paid for by KUMC. *The University of Kansas Medical Center is proud to be an Equal Opportunity/Affirmative Action Employer.*

NEW YORK STATE INSTITUTE FOR BASIC RESEARCH IN DEVELOPMENTAL DISABILITIES

STAFF RESEARCH SCIENTISTS (four positions): will be hired to complement and strengthen the New York State Institute for Basic Research (IBR) in Developmental Disabilities' ongoing clinical and research studies of autism. The successful applicants will have an established research program and nationally recognized contributions related to autism in one or more of the following areas: neurobiology, molecular biology/genetics, biochemistry, and child psychology/applied behavior analysis. Positions are open until filled. Compensation will be commensurate with experience in accordance with conditions set by the New York State Department of Civil Service with salary range of $70,000 to $140,000. New York State offers an excellent benefits package. Please submit curriculum vitae indicating position of interest to: **Dr. Ted Brown, Director, Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, NY 10314, fax: 718- 494-7917,** or by **e-mail: ted.brown@omr.state.ny.us.**

POSTDOCTORAL POSITION

A NIH-funded position in enzymology is available in the laboratory of **Dr. Marilyn Jorns** at Drexel University College of Medicine, Philadelphia, Pennsylvania. The position involves mechanistic studies on nikD, a flavoenzyme important in the biosynthesis of nikkomycin antibiotics **(website: http://www.drexelmed.edu/documents/biochemistry/faculty/resume_jorns.htm).** Candidates must have experience in protein purification, enzyme kinetics, and mutagenesis. Please forward curriculum vitae and the names/contact information of three references to **e-mail: marilyn.jorns@drexelmed.edu.**

ILLINOIS
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

The Department of Natural Resources and Environmental Sciences at the University of Illinois at Urbana-Champaign seeks a full-time (9-month), tenure-track Assistant Professor of Spatial Landscape Analysis and Management with a 40% teaching, 60% research allocation of effort. Applicants must have a Ph.D. in a discipline related to environmental science, and who will be able to develop a creative and integrative program on spatial analysis and management of ecosystems at the landscape level. Successful candidates will be able to collaborate with faculty in a wide variety of disciplines, train and direct undergraduate and graduate students in spatial analysis, develop an internationally recognized research program, contribute to teaching needs, and successfully compete for research funds.

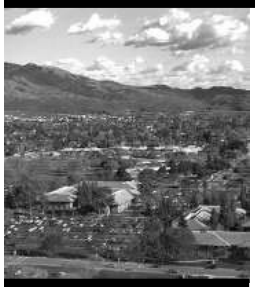
More information and application information is posted on **http://www.nres.uiuc.edu/careers/nresjobs.html** or **217-244-1484**.

Deadline to apply is **January 15, 2007**.

UIUC is an AA/EO Employer.

JGI
DOE JOINT GENOME INSTITUTE
US DEPARTMENT OF ENERGY
OFFICE OF SCIENCE

Plant Biologist / Staff Scientist



The DOE Joint Genome Institute (DOE JGI), supported by the U.S. Department of Energy Office of Science, unites the expertise of several DOE national laboratories, to advance genomics in support of the DOE missions related to clean energy generation and environmental characterization and clean-up. Additional information about DOE JGI can be found at: **www.jgi.doe.gov**.

The Department of Energy Joint Genome Institute (DOE JGI) located in Walnut Creek, CA (San Francisco Bay Area) is seeking a highly experienced Plant Genetics Scientist. The successful candidate will serve as a Staff Scientist in a newly formed Plant Biology group and will lead a significant scientific research initiative focusing on some aspects of plant genetics or the functional genomics of plants. The individual will also provide scientific guidance to the JGI regarding the biological applications of plant genomic sequences, and represent the JGI in contacts with internal and external organizations and funding agencies.

The JGI is a large-scale Production Genomics Facility involving partnerships with several DOE national laboratories. The JGI has extensive DNA sequencing capabilities - currently greater than 3 billion raw bases per month - and a strong internal informatics infrastructure.

High depth, draft, and finished genome sequences have already been completed for many species including Poplar Trichocarpa and numerous plant pathogens. Sequencing of a large number of bioenergy feedstocks are also currently underway. The JGI has established scientific groups in Computational Genomics, Genomic Technologies, Microbial Ecology, Genome Biology, and Genetic Analysis. The JGI is now seeking to augment these capabilities with a significant program in Plant Genomics. For detailed information about the JGI go to: **www.jgi.doe.gov**.

QUALIFICATIONS: A Ph.D. in Plant Genetics or a closely related discipline is required. Significant research work beyond the degree is expected and documented by a strong publication record. Demonstrated excellence in leadership and management of complex research efforts and demonstrated capacity to do innovative and applied work will be necessary, and the candidate must be able to establish collaborative research with internal principal investigators and other funding institutions and effectively present and promote research.

NOTE: This is a full-time two-year term appointment through the Lawrence Berkeley National Laboratory with possible renewal contingent upon satisfactory job performance and continuing availability of funding. To apply, please include a letter of research intent, CV, and the names of three to five professional references and forward to wrcannan@lbl.gov or mail or fax materials to Bill Cannan/Sr. Recruiter, Human Resources Department, DOE Joint Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA, 94598 (Fax 925-296-5656). Please reference job number **20052** in your cover letter. We are an Equal Opportunity Employer with a commitment to workforce diversity.

Faculty Positions in Environmental Health
Center for Environmental Health
Indiana University School of Medicine

The newly established Indiana University Center for Environmental Health located in the IU School of Medicine in Indianapolis announces a search for new faculty in the area of environmental health. The Center for Environmental Health, in partnership with the Department of Pharmacology and Toxicology and the Indiana University Cancer Center seeks outstanding individuals for tenure-track faculty positions at the Assistant, Associate and Full Professor level. The Center for Environmental Health is partnering with current active programs of excellence in toxicology, cancer research, neuropharmacology, and children's health to address mechanisms of action and genetic susceptibility to environmental influences.

A Ph.D. and/or M.D. degree and at least three (3) years of postdoctoral research experience are required, and strong evidence of productivity and grant support are desirable. Competitive start-up packages include ample space and access to exceptional core research facilities. Successful candidates will be expected to develop strong extramurally supported research programs, contribute to an already strong, collaborative research environment, and to excel in mentoring graduate and postgraduate trainees. More information about the Center for Environmental Health and partner departments can be found on our websites: **http://ceh.iu.edu; http://pharmtox.iusm.iu.edu** and **http://cancer.iu.edu**.

Interested individuals should submit a curriculum vitae, a research prospectus, and the names and addresses of three (3) references. Application materials should be submitted electronically to the attention of **Dr. James E. Klaunig**, Robert B. Forney Professor of Toxicology, Director, Center for Environmental Health, IU School of Medicine at **cehinfo@iu.edu**.

We encourage applications from women and other underrepresented groups. In addition, it is the University's policy to provide reasonable accommodations for qualified persons with disabilities. Indiana University is an EEO/AA Employer, M/F/D.

Max Planck Institute for the Physics of Complex Systems

mpipks

The Max Planck Institute for the Physics of Complex Systems (MPIPKS) seeks one

DISTINGUISHED PKS POSTDOCTORAL FELLOW

The successful candidate will complement research areas pursued at the institute and conduct independent studies e.g. in the following fields: Matter at ultralow temperatures, molecular electronics, statistical physics far from equilibrium, soft condensed matter, sensory systems, and genetic and metabolic networks. Novel directions with promising perspectives are welcome as well.

Further details of research opportunities can be found on our web-site: http://www.pks.mpg.de.

The appointment requires an entry age of less than 35 and is typically for two years, renewable for one more year. Please send a CV with a list of publications and a statement of research interests by e-mail to: visitors@mpipks-dresden.mpg.de or by post to the following address:

Prof. Dr. Frank Jülicher
Max Planck Institute
for the Physics of Complex Systems
Nöthnitzer Str. 38, 01187 Dresden, Germany

Please also arrange for three letters of reference to be sent directly to the address mentioned above.

Application deadline is February 9, 2007.

MAX-PLANCK-GESELLSCHAFT

POSITIONS OPEN

TENURE-TRACK FACULTY POSITION
Department of Cellular and Integrative Physiology
Indiana University School of Medicine

The Department seeks applicants for a tenure-track position at the **ASSISTANT PROFESSOR** level, although strong candidates at higher rank will be considered. Applicants must have an M.D. or Ph.D. degree, at least three years of postdoctoral experience, high quality peer-reviewed publications, evidence of independent research, and competitive funding potential. We seek innovative scientists using molecular, cellular, or whole animal approaches with expertise in areas that will complement research strengths in the Department. Areas include cytoskeleton, mechanotransduction, smooth muscle, growth, apoptosis, membranes, diabetes, and neurosecretion. Although preference will be given to the above, highly qualified candidates in other areas of research will be considered. Successful applicants will be expected to maintain an extramurally funded research program and participate in the teaching of medical and graduate students. Significant resources available include competitive startup package, newly renovated laboratory space, and long-term research and salary incentives. Further information can be found at **website: http://www.iupui.edu/~medphys.** Application deadline for the first review of applications will be January 5, 2007, and the review will continue until the position is filled.

Applicants should send (in electronic format only) their curriculum vitae, brief statement of research interests and goals, and the names of three references to: **Dr. Michael Sturek, Chair, Department of Cellular and Integrative Physiology, c/o Marlene Brown (e-mail: pbio@iupui.edu), 635 Barnhill Drive, M.S. 385, Indianapolis, IN 46202-5120.** *Indiana University is an Equal Employment Opportunity/Affirmative Action Employer.*

FACULTY POSITION ASSISTANT/ ASSOCIATE PROFESSOR
Pharmacology

The College of Veterinary Medicine at the University of Georgia is seeking a **PHARMACOLOGIST or TOXICOLOGIST** for a tenure-track position in the Department of Physiology and Pharmacology. The successful candidate will be expected to develop and maintain an externally funded research program and participate in teaching pharmacology to veterinary students in the professional program. Qualifications for the position include a Ph.D., M.D., D.V.M., or equivalent degree. Current program strengths within the Department include molecular and cellular physiology, endocrinology, vascular physiology and pharmacology, toxicology and neuroscience. While we seek candidates who will complement existing research activity, evidence of research excellence is more important than the specific area of study. See **website: http://www.vet.uga.edu/vph/** for more information. Interested applicants should submit a letter of application including a statement of research plans, a statement of teaching interests, curriculum vitae, and the names and contact information for three references to: **Dr. John Wagner, Chair of the Search Committee, College of Veterinary Medicine, University of Georgia, 501 D.W. Brooks Drive, Athens, GA 30602,** or electronically to **e-mail: jwagner@vet.uga.edu.** Applications received by January 19, 2007, are assured full consideration. *The University of Georgia is an Equal Opportunity/Affirmative Action Employer.*

POSTDOCTORAL POSITION in molecular neuropharmacology available early 2007 to study the regulation of survival signaling in the brain by pharmacological and behavioral interventions (funded by the National Institute for Mental Health). Experience with histological techniques, molecular biological methods, and Western analysis desirable. Please send curriculum vitae with names of three references and a statement of research interests to: **Dr. Amelia Russo-Neustadt. Telephone: 323-343-2074. E-mail: arusson@calstatela.edu.**

POSITIONS OPEN

The Department of Pharmacology and Physiology at the University of Rochester Medical Center seeks applications for a full-time, tenure-track position at the rank of **ASSISTANT PROFESSOR.** Outstanding candidates qualified for higher ranks will also be considered. Competitive applicants will have a Ph.D. or equivalent degree, postdoctoral training, and a clear record of research productivity and creativity.

We are interested in applicants whose research program will complement existing faculty research strengths in transmembrane signaling, which include: cell surface receptors, ion channels, G-proteins, calcium signaling, scaffolding proteins and signaling mechanisms in mitochondria and endoplasmic reticulum. Applicants working in all fields are encouraged to apply, but particular interests include those working in neuroscience, cardiovascular disease, endocrinology, and chemical biology. The successful applicant will receive a competitive startup package and be expected to develop a dynamic, well-funded research program and contribute to graduate and medical teaching programs.

The University of Rochester Medical Center continues to undergo a major expansion in basic and translational research. Additional information about the University, the Department and faculty research interests can be found at **website: http://www.urmc.rochester.edu/phph.**

Please send curriculum vitae, a brief statement of research plans, reprints of three key publications, and three letters of recommendation to: **Dr. A. William Tank, Chair, Search Committee, Department of Pharmacology and Physiology, P.O. Box 711, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642.** *The University of Rochester is an Equal Opportunity Employer.*

ASSISTANT PROFESSOR
Youngstown State University

BIOLOGICAL SCIENCES. Tenure-track Assistant Professor position available August 2007. Ph.D. in animal physiology, comparative physiology, or related field required. Postdoctoral research experience preferred. Successful candidate is expected to develop a competitive research program in animal (systems) physiology capable of securing extramural funding, have a strong commitment to training undergraduate and graduate students, and have a strong commitment to teaching. Teaching responsibilities include courses in general biology, anatomy and physiology, and comparative physiology.

Send letter of interest, curriculum vitae, transcripts, and the names, addresses, and telephone numbers of three references to: **Dr. Mark D. Womble, Search Committee Chairperson, Biological Sciences, Youngstown State University, Youngstown, OH 44555. E-mail: mdwomble@ysu.edu.**

Applications received by January 15, 2007, will receive full consideration; however, review of applications will continue until position is filled. For complete posting, information, and hiring requirements visit **website: http://www.cc.ysu.edu/hr.**

Youngstown State University is an Affirmative Action/ Equal Opportunity Employer committed to increasing the diversity of its faculty, staff, and students.

UNIVERSITY OF CALIFORNIA, MERCED
School of Engineering: Bioengineering

SENIOR FACULTY. Unique opportunity for distinguished, visionary, pioneering, collaborative individuals to join the faculty in the School of Engineering at the new University of California campus. The research area within bioengineering is open; individuals with research interests that include cellular/tissue engineering, microfluids, biomaterials, bioinstrumentation, sensor development; systems physiology/biology are particularly encouraged to apply. For more information, or to submit your application, please visit our **website: http://jobs.ucmerced.edu/n/academic/position.jsf?positionId=695.** *Affirmative Action/Equal Opportunity Employer.*

POSITIONS OPEN

ASSISTANT PROFESSOR/SCIENCE EDUCATION
Department of Biology
Ball State University
Muncie, Indiana

Tenure-track position available August 17, 2007. Responsibilities: teach undergraduate and graduate courses in elementary and secondary grades science methods and introductory biology for elementary education majors; promote student involvement in departmental academic activities. Minimum qualifications: earned doctorate in science education or related field with strong background in the life sciences earned by November 1, 2007; teacher certification or licensure; at least one year of full-time teaching experience at the elementary or secondary level; effective written and oral communication skills. Preferred qualifications: demonstrated teaching ability and publications and/or evidence of other scholarly activity; experience with and a commitment to one or more of the following: (a) working in professional development schools; (b) using technology as a tool for teaching and learning; (c) participating in interdisciplinary collaborations.

Send letter of application, curriculum vitae, documentation of scholarly activity, transcripts, and three letters of reference to: **Dr. Melissa Mitchell, Chair, Science Education Search Committee, Department of Biology, Ball State University, Muncie, IN 47306.** Review of applications will begin immediately and will continue until the position is filled. **(Website: http://www.bsu.edu.)** *Ball State University is an Equal Opportunity, Affirmative Action Employer and is strongly and actively committed to diversity within its community.*

FACULTY FELLOW
Environmental Science

The Department of Biology seeks a broadly trained **ECOLOGIST/ENVIRONMENTAL SCIENTIST** to teach environmental science, an Earth charter seminar, and an intercultural studies course focusing on environmental quality/sustainable development. Ph.D. (completed by 15 August 2007) required. Preference given to individuals with experience in interdisciplinary environmental studies and ability to teach an upper-division botany course, e.g., plant anatomy or physiology. Sponsored jointly with the Center for Women's Intercultural Leadership, the appointment is for one year, possibly renewable for a second year. Saint Mary's College is an undergraduate women's College with a liberal arts tradition and affiliation with the Roman Catholic Church. Evaluation of candidates will begin February 1, 2007, and continue until position is filled. Send curriculum vitae, statement of teaching and research goals, and names and contact information (including e-mail) of three references to: **Dr. Richard J. Jensen, Chair, Environmental Science Search Committee, Department of Biology, Saint Mary's College, Notre Dame, IN 46556.** Visit **website: http://www.saintmarys.edu/~hr/employmentopps.html** for additional details. *Women and scholars from underrepresented groups are encouraged to apply. Equal Opportunity Employer.*

COMPUTATIONAL BIOLOGIST

The Department of Biochemistry and Biophysics at the University of Rochester Medical Center invites applications for a tenure-track position at the **ASSISTANT PROFESSOR** level or higher. Emphasis will be on applicants with experience in computational biology, systems biology, or bioinformatics. To apply, submit curriculum vitae, statement of research accomplishments and plans, three reprints, and three letters of recommendation to: **Gail Marriott, Computational Biology Search, Department Department Biochemistry and Biophysics, P.O. Box 712, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642. E-mail: gail_marriott@urmc.rochester.edu.** See **website: http://dbb.urmc.rochester.edu** for Department information. *The University of Rochester is an Equal Opportunity/Affirmative Action Employer.*

AWARDS

CALL FOR NOMINATIONS

ROBERT J. AND CLAIRE PASAROW FOUNDATION
20th Annual
MEDICAL RESEARCH AWARDS

Cancer, Cardiovascular Disease, Neuropsychiatry

Congratulations to:
2002 Pasarow Award Winner and 2006 Nobel Laureate in Chemistry, Roger Kornberg
2003 Pasarow Award Winner and 2006 Lasker Prize Winner, Elizabeth Blackburn

The Foundation has established three yearly medical prizes for distinguished accomplishment in research in order to increase public awareness of vital areas of investigation. This is the twentieth year of the awards program. Each award is for $50,000, presented directly to the awardee. The three prizes – one in each of the three fields – are given for extraordinary basic and/or clinical research.

Cancer: including basic cellular processes and the various forms of cancer. **Past awardees:** Peter K. Vogt, PhD, Irving L. Weissman, MD, George F. Vande Woude, PhD, Erkki Ruoslahti, MD, Harold N. Weintraub, MD, PhD, Ronald M. Evans, PhD, Stanley J. Korsmeyer, MD, Carlo M. Croce, MD, Alfred G. Knudson, Jr., MD, PhD, Robert A. Weinberg, MD, Eric S. Lander, D.Phil., Paul L. Modrich, PhD, Anthony S. Fauci, MD, Alexander J. Varshavsky, PhD, Tom Maniatis, PhD, Roger D. Kornberg, PhD, Elizabeth H. Blackburn, PhD, Fred W. Alt, PhD, and Bert O'Malley, MD.

Cardiovascular Disease: including disorders of the heart and vascular system. **Past awardees:** Burton E. Sobel, MD, Harvey Feigenbaum, MD, Bernardo Nadal–Ginard, MD, PhD, Mordecai P. Blaustein, MD, Jonathan Seidman, PhD and Christine Seidman, MD, Glenn A. Langer, MD, Philip Majerus, MD, Jan L. Breslow, MD, Kenneth R. Chien, MD, PhD, Michael A. Gimbrone, Jr., MD, Masashi Yanagisawa, MD, PhD, Mark T. Keating, MD, Eric N. Olson, PhD, Richard P. Lifton, MD, PhD, Robert J. Lefkowitz, MD, Shaun Coughlin, MD, PhD, Judah Folkman, MD, Barry S. Coller MD, and Douglas C. Wallace, PhD.

Neuropsychiatry: including neuroscience of neurologic and mental disorders. **Past awardees:** Nancy Wexler, PhD, Eric R. Kandel, MD, Floyd E. Bloom, MD, Solomon H. Snyder, MD, Michael E. Phelps, PhD, Patricia S. Goldman-Rakic, PhD, Huda Akil, PhD and Stanley Watson, MD, PhD, Arvid Carlsson, MD, PhD, Stanley B. Prusiner, MD, Joseph T. Coyle, MD, Eric J. Nestler, MD, PhD, Fred H. Gage, PhD, Michael I. Posner, PhD and Marcus E. Raichle, MD, Pasko Rakic, MD, PhD; Seymour Benzer, PhD, Tomas Hökfelt, MD, PhD, Thomas M. Jessell, PhD, Judith L. Rapoport, MD, and Bruce McEwen, PhD.

The criterion for the Pasarow Medical Research Awards is evidence of extraordinary accomplishment and the likelihood of continuing outstanding achievement in biomedical science.

Nominators for the 2006 Award should provide a letter of no more than one page stating the rationale for the nomination and a copy of the nominee's curriculum vitae and bibliography in NIH format. Applications will be reviewed by the Board of Directors in consultation with various medical scholars. Members of the Board of Directors are **Jack D. Barchas**, MD, President and Chairman; **Claire Pasarow**, Chief Financial Officer; **Brian E. Henderson, MD** – University of Southern California; **Anthony H. Pasarow** – San Pedro, California; **Susan Pasarow, MSW** – Lake Oswego; **Judith L. Swain, MD** – UCSD; **Joseph P. Van Der Meulen, MD** – University of Southern California, and **Alexander J. Varshavsky, PhD** – CalTech.

Nominations should be sent to: **Robert J. and Claire Pasarow Foundation, c/o Jack D. Barchas, MD, Weill Medical College, Cornell University, 1300 York Avenue, Box 171, Room F–1231, New York, NY 10021**.

For more information, please see **www.pasarowfoundation.org**. Inquiries can be addressed to **Jack D. Barchas, MD** at **(212) 746–3770** or **nominations@pasarowfoundation.org**. Nominations should be received by **January 19, 2007**.

POSITIONS OPEN

ENDOWED CHAIR IN THE BIOCHEMICAL SCIENCES
Department of Chemistry
University of Missouri, Rolla

Distinguished scientists are encouraged to apply for the **Richard K. Vitek**/Foundation for Chemical Research, Incorporated (FCR) Endowed Chair in Biochemistry, including the areas of bioorganic, bioinorganic, biophysical, or biomaterials chemistry at the University of Missouri, Rolla (UMR). The new position carries a very generous endowment, which can be used in part to support the research of the Chair. The Richard K. Vitek/FCR Endowed Chair in Biochemistry will provide important leadership for UMR's targeted growth in the biosciences. A new biosciences building has been established by the state of Missouri as the next capital improvement project for higher education.

The successful candidate should have a doctorate in chemistry, biochemistry, or a related field, and have an outstanding international reputation and publication record, and a substantial record of extramural funding. Review of applications will begin on January 15, 2007, and continue until the position is filled. For further information, we encourage you to visit our **website: http://chem.umr.edu** or contact **Professor Jay A. Switzer** at **e-mail: jswitzer@umr.edu.**

Please submit curriculum vitae along with short summaries of past research accomplishments and future research directions to: **Human Resource Services, Reference Number: 00033199, University of Missouri-Rolla, 1870 Miner Circle, Rolla, MO 65409-1050.**

UMR is an Affirmative Action/Equal Opportunity Employer. Women, minorities, and persons with disabilities are encouraged to apply.

POSTDOCTORAL POSITIONS
Molecular Cell Biology of Diabetic Complications

As reviewed in *Nature* **414:**813, 2001, our laboratory focuses on the mechanisms by which hyperglycemia causes vascular damage. We are currently investigating (a) the molecular basis for "metabolic imprinting," (b) the genetic basis for familiar clustering of susceptibility to hyperglycemic damage, (c) endothelial progenitor cell dysfunction and impaired vasculogenesis in diabetes, and (d) identification of novel therapeutic strategies for preventing metabolite-induced vascular damage. Candidates should have a strong foundation in molecular and cell biology. Please send curriculum vitae and names/contact information of three references to:

Dr. M. Brownlee
Diabetes Research Center
Albert Einstein College of Medicine
Jack and Pearl Resnick Campus
1300 Morris Park Avenue
Bronx, NY 10461
E-mail: brownlee@aecom.yu.edu

Equal Opportunity Employer.

DIRECTOR
Species Program NatureServe

NatureServe is seeking a leader in the field of species conservation, systematics, or biodiversity informatics to oversee continued development and use of the organization's highly regarded botanical and zoological databases. This senior-level position will be involved in developing scientific methods, analytical tools, and information products designed to ensure that high-quality species data are available to inform and improve conservation and resource management decisions. Requirements include a Ph.D. in zoology, botany, conservation biology, or related discipline, and a proven track record in fundraising, program management, and partnership-building. Full position description is available at **website: http://www.natureserve.org/job/jobNSspeciesprogram.jsp.** Send letter of interest, curriculum vitae, and three references to: **Species Director Search, NatureServe, 1101 Wilson Boulevard, Arlington, VA 22209. E-mail: jobs@natureserve.org.** *NatureServe is an Equal Opportunity Employer.*

WOODS HOLE OCEANOGRAPHIC INSTITUTION

A new facility dedicated to Fourier-transform ion cyclotron resonance mass spectrometry (FT-ICR MS) in the Earth sciences will be established at the Woods Hole Oceanographic Institution (WHOI). We seek a motivated individual to serve as the **MANAGER** of this facility.

Anticipated responsibilities include, but are not limited to: financial management for facility, instrument maintenance, supervision of facility users, informal education of graduate students and postdoctoral researchers in FT-ICR MS, and development of methods for sample analysis and data processing.

The successful candidate should have a M.S. or Ph.D. in analytical chemistry or a related field. In the absence of a formal degree, considerable equivalent work experience is required.

Preferred candidates will have (1) experience with FT-ICR MS, preferably in the areas of instrument and technique development; (2) knowledge of analysis of large data-sets from proteomic and/or metabolomic studies, and (3) superb organizational and communication skills.

Consideration of applications will begin after January 15, 2007. Education and experience will determine level of hire.

To begin the online application process, please visit **website: http://jobs.whoi.edu.** WHOI is a smoke-free workplace. *Equal Opportunity Employer.*

ASSISTANT, ASSOCIATE, OR FULL PROFESSOR
Tenure-Track Joint Position
California State University, Los Angeles

This position is in the Department of Mathematics and the Department of Biological Sciences. Applications are invited starting September 2007 (rank of position commensurate with experience). Candidate is expected to establish an independent research program involving undergraduate and M.S. students. Those with strong applied mathematics skills and academic/industrial postdoctoral research experience in bioinformatics or computational biology will be given preference. Ability to teach a range of undergraduate and graduate (M.S.) courses in mathematics and biology relevant to the candidate's experience is essential. Publications in peer-reviewed journals and/or grant activity is required. Send letter of application, curriculum vitae, three letters of recommendation, and official transcript from Institution awarding Doctorate to: **Dr. P. K. Subramanian, Chair, Department of Mathematics, California State University at Los Angeles, 5151 State University Drive, Los Angeles, CA 90032.** *An Equal Opportunity, Title IX, Disabled, Employer.*

POSTDOCTORAL FELLOWSHIP

Physics-based **COMPUTATIONAL BIOLOGIST** sought to probe detailed molecular structures of apolipoprotein (apo) A-I on high density lipoprotein (HDL). Focus is on pathways for in vivo assembly of cholesteryl ester (CE)-rich (spheroidal) HDL, including the structure/dynamics of phospholipid (PL)-poor (preβ) and PL-rich (discoidal) HDL. The driving hypothesis is that apoA-I is a uniquely elastic lipid-clamp capable of absorbing PL and CE in increments of a few molecules at a time. Because of a recent demonstration by our laboratory of the power of molecular dynamics (MD) simulations to provide supramolecular images of HDL, MD simulations combined with experimental approaches uniquely position us to gain fundamental new insights into the structure/function of HDL subspecies. Candidates should have obtained a Ph.D. within the past three years with a strong background in molecular modeling/dynamics. A highly motivated and independent scientist able to work within an interdisciplinary team is preferred. E-mail research summary, curriculum vitae, and three references to: **Jere P. Segrest, e-mail: segrest@uab.edu.**

FACULTY POSITIONS
Georgia Institute of Technology
College of Computing
Computational Science and Engineering Division

The Computational Science and Engineering division within the College of Computing at the Georgia Institute of Technology invites applications for tenure-track faculty positions. Applications at all levels of service will be considered. Applicants must have an outstanding record of research, a sincere commitment to teaching, and interest in engaging in substantive interdisciplinary research with collaborators in other disciplines. Candidates with demonstrated expertise in high-performance computing (HPC) in support of applications from biology or other areas of science and engineering are encouraged to apply.

Reviews of submitted applications begin December 15, 2006. We expect most hiring decisions will be made by May 1, 2007.

We strongly encourage application cover letters and materials be submitted online by going to **website: http://www.cc.gatech.edu/recruiting/** or by **e-mail: recruiting@cc.gatech.edu.** If done by e-mail, the cover letter must include a URL pointing to application materials in PDF. The application material should include full academic curriculum vitae, teaching and research statements, a list of at least three references, and up to three publications. Applicants are encouraged to clearly identify in their cover letter the area(s) that best describe their research interests.

Georgia Tech is an Affirmative Action/Equal Opportunity Employer. Applications from women and underrepresented minorities are strongly encouraged.

STATISTICAL/QUANTITATIVE GENETICS AND GENOMICS

The Departments of Animal Science and Fisheries and Wildlife at Michigan State University invite applications for an academic year, tenure-track position in statistical/quantitative genetics and genomics at the **ASSISTANT PROFESSOR** level. The successful candidate will develop a strong extramurally supported research program at the interface among statistical, quantitative, and molecular genetics, focusing on applications to domestic and natural animal populations. Extensive collaboration with empirical animal geneticists and biologists in faculties of both Departments is expected. Refer to **website: http://www.ans.msu.edu** for more details. A cover letter, curriculum vitae, statements of research interests and teaching philosophy, examples of scientific writing, and three letters of reference should be sent by January 31, 2007, to: **Dr. Robert J. Tempelman, c/o Kathy Tatro, Department of Animal Science, 1290 Anthony Hall, Michigan State University, East Lansing, MI 48824-1225. Telephone: 517-355-8417.** Application materials can also be e-mailed to **e-mail: tatro@msu.edu.** *Michigan State University is an Equal Opportunity/Affirmative Action Employer.*

WILDLIFE ECOLOGIST
Illinois Natural History Survey

Wildlife Ecologist, **ASSISTANT PROFESSIONAL SCIENTIST.** Conduct research on terrestrial vertebrates in urban and suburban environments (including urban landscape ecology, human-wildlife interactions, and/or adaptive responses to urban environments) with applicability to Illinois and United States. Requires a Ph.D. (by starting date) in an appropriate discipline. Responsibilities: develop vigorous, externally funded research program; collaboration with state, federal, and private organizations and the University of Illinois; publish research findings in scientific journals; participate in outreach programs to public and relevant stakeholders. Illinois Natural History Survey is part of the Illinois Department of Natural Resources and an Affiliated Agency of the University of Illinois at Urbana-Champaign. For complete position description and application requirements visit our **website: http://www.inhs.uiuc.edu/opportunities.**

THE 2007 LOUISA GROSS HORWITZ PRIZE FOR BIOLOGY OR BIOCHEMISTRY

COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK

The Louisa Gross Horwitz Prize was established under the will of the late S. Gross Horwitz through a bequest to Columbia University and is named to honor the donor's mother. Louisa Gross Horwitz was the daughter of Dr. Samuel David Gross (1805-1889), a prominent surgeon of Philadelphia and author of the outstanding Systems of Surgery who served as President of the American Medical Association.

Each year since its inception in 1967, the Louisa Gross Horwitz Prize has been awarded by Columbia University for outstanding basic research in the fields of biology or biochemistry. The purpose of this award is to honor a scientific investigator or group of investigators whose contributions to knowledge in either of these fields are deemed worthy of special recognition.

The Prize consists of an honorarium and a citation which are awarded at a special presentation event. Unless otherwise recommended by the Prize Committee, the Prize is awarded annually. Dr. Roger Kronberg, Stanford University in Stanford, CA was the 2006 awardee.

QUALIFICATIONS FOR THE AWARD

The Prize Committee recognizes no geographical limitations. The Prize may be awarded to an individual or a group. When the Prize is awarded to a group, the honorarium will be divided among the recipients, but each member will receive a citation. Preference will be given to work done in the recent past.

Nominations must be submitted electronically at: http://cumc.columbia.edu/horwitz/

Nominations should include:

1. A summary, preferably less than 500 words, of the research on which this nomination is based.
2. A summary, preferably less than 500 words, of the significance of this research in the fields of biology or biochemistry.
3. A brief biographical sketch of the nominee, including positions held and awards received by the nominee.
4. A listing of up to ten of the nominee's most significant publications relating to the research noted under item 1.
5. A copy of the nominee's curriculum vitae.

Nominations must be submitted no later than **January 31, 2007.**

Fundación **BBVA**

Fourth Call

Environmental Research Grants

The BBVA Foundation supports scientific research oriented to the preservation of biodiversity.

Ecology and Conservation Biology

Maximum no. of grants: 12 - Maximum funding per project: €200,000 - Maximum duration: 3 years

Priority areas:

- Molecular, genetic and physiological studies with a conservation focus.
- Application of new methods and techniques in ecology and conservation biology.
- Restoration ecology and predictive analysis of ecosystem recovery.
- Habitat deterioration and fragmentation.
- Evolutionary ecology, co-evolution and behavioural ecology with a conservation focus.
- Impacts of pollution on populations and communities and their remediation.
- Molecular microbiology for ecosystem protection and restoration.
- Dynamics and management of endangered species and populations.
- Ethnobiology and sustainable development.
- Design, conservation and management of protected natural spaces.
- Global change and biodiversity conservation.

This call is directed at research projects involving international cooperation, especially with Latin America.

Deadline for submissions:
31 January 2007

Conditions and information:
www.fbbva.es
convocatorias@fbbva.es

Fundación BBVA
Gran Vía, 12
48001 BILBAO - SPAIN
Fax: (34) 94 424 46 21

Paseo de Recoletos, 10
28001 MADRID - SPAIN
Fax: (34) 91 374 34 44

POSITIONS OPEN

ORGANISMAL BIOLOGIST

The Biology Department of Wilkes University invites applications for a tenure-track position in biology at the **ASSISTANT PROFESSOR** level, starting August 2007. We seek a broadly trained Organismal Biologist with research experience and teaching ability in one or more of the following areas: conservation biology, population genetics, phylogenetics, biostatistics, landscape or ecosystems ecology, or functional morphology, to complement existing strengths in plant ecology, plant physiology, and animal behavior. We seek an individual who is dedicated to innovative teaching and research in an undergraduate setting. Responsibilities will include upper-level courses in area of expertise, participation in general biology, and research activities to enhance a new Institute of the Environment. A Ph.D. is required, postdoctoral experience is preferred. The successful candidate will be expected to develop a strong research program involving undergraduates. Applicants should provide digital copy of application letter, curriculum vitae, statements of teaching and research goals, reprints (PDF), and three reference letters to: **Dr. Ken Klemow, Search Chair (e-mail: kklemow@wilkes.edu).** A separate copy of application letter and curriculum vitae should be sent to: **Wilkes University (Reference # BI0006), P.O. Box 3924, Scranton, PA 1505.** Application review will begin January 8, 2007. *Wilkes University is an Equal Opportunity/Affirmative Action Employer committed to a diverse faculty, staff, and student body. Women and minority candidates are strongly encouraged to apply.*

FACULTY POSITION, MICROBIAL ECOLOGY/PHYSIOLOGY

Miami University invites applications for a tenure-track **ASSISTANT PROFESSOR** position in microbiology, with a research emphasis in microbial ecology and/or environmental microbiology, with a background in microbial physiology, to begin in August 2007. Applicants must have a doctorate in microbiology or closely related field, and postdoctoral research experience. Responsibilities will include maintaining an externally funded research-active laboratory, directing M.S. and Ph.D. students, teaching undergraduate and graduate courses, including microbial ecology, and microbial physiology or general microbiology, and service to the University. More information about the Department of Microbiology and Miami University is available at **website: http://www.cas.muohio.edu/micro/.** Screening of applications will begin on January 1, 2007, and continue until the position is filled. Applicants should submit curriculum vitae, three reprints, statement of research interests and goals, statement of teaching philosophy, and have three letters of reference sent to: **Dr. Gary R. Janssen, Department of Microbiology, Miami University, Oxford, OH 45056. E-mail: janssegr@muohio.edu.** Campus crime and safety report, **website: http://www.muohio.edu/righttoknow.** Hard copy available upon request. *Miami University is an Equal Opportunity Employer/Affirmative Action Employer.*

RESEARCH FELLOWSHIPS
Australian Research Council
Centre of Excellence, Australia

The Australian Research Council Centre of Excellence for Coral Reef Studies is an international research centre, administered by James Cook University, in partnership with the Australian National University, the University of Queensland, and 23 other institutions and industry partners in nine countries. The following three-year Research Fellowship Positions are available: (1) biodiversity of coral reefs, (2) tropical marine palaeoecology, and (3) modelling of coupled social-ecological systems.

Closing date is 12 January 2007.

Details available from **website: http://www.coralcoe.org.au/employment.html.**

Equal Opportunity in Employment is University policy.

The University reserves the right to invite applications or not to make an appointment.

POSITIONS OPEN

RESEARCH SCIENTIST: STROKE/ CEREBRAL ISCHEMIA

The Central Illinois Neuroscience Foundation (CINF), a nonprofit foundation dedicated to the enhancement of neurological health through education and research, seeks a researcher to oversee its preclinical stroke/cerebral ischemia laboratory affiliated with the Department of Biological Sciences and the Program of Excellence in Neuroscience and Behavior at Illinois State University (ISU).

Qualifications include: (1) a Ph.D. or its equivalent in neuroscience, neurobiology, or a related field, (2) at least five years of experience studying stroke or ischemia in the laboratory, (3) a strong publication record in stroke, cerebral ischemia, or related fields, (4) the ability to develop a research program that utilizes the intraluminal thread model of focal cerebral ischemia in rodents to study neurodegeneration, neuroprotection, neuroregeneration, or functional recovery, (5) previous experience in attracting extramural research funding, and (6) the ability to mentor biology graduate students (M.S. and Ph.D.) and neurosurgical residents in preclinical stroke research.

The position offers the opportunity for adjunct faculty appointment at Illinois State University, the chance for interaction with a diverse array of neuroscientists at ISU **(website: http://lilt.ilstu.edu/POENB/)**, and clinical research possibilities at local hospitals and clinics through collaboration with local physicians and CINF's clinical research staff.

The position also provides access to a well-equipped laboratory and rodent animal care facility, a graduate research fellowship, and initial intramural funding of research expenses.

This is a full-time, 12-month appointment with competitive benefits, and a salary commensurate with experience. The anticipated start date is winter/spring 2007, based upon availability of the successful applicant.

Interested applicants should submit curriculum vitae and a letter describing their research interests along with three (p)reprints of publications, and arrange for three letters of recommendation to be sent to: **Research Scientist Search, Central Illinois Neuroscience Foundation, 1015 South Mercer Avenue, Bloomington, IL 61701.** Review of applications will begin immediately and continue until the position is filled. For more information about CINF visit our **website: http://cinf.org.** *CINF is an Equal Opportunity Employer.*

The Office of Science, Department of Energy is seeking a motivated and highly qualified individual to serve as the **ASSOCIATE DIRECTOR,** Office of Biological and Environmental Research. As such, you will provide leadership and direction in establishing vision, strategic plans, goals, and objectives for the research activities supported. You may apply through two different methods, one is for a **SENIOR EXECUTIVE SERVICE** appointment and the second is for an **INTERGOVERNMENTAL PERSONNEL ACT** appointment. The announcement number is SES-SC-HQ-005. The announcement opens on November 6, 2006, and closes on December 21, 2006. Visit **website: http://www.usajobs.opm.gov/** for more information and for instructions concerning application procedures.

A **POSTDOCTORAL POSITION** is open to study the role of ubiquitylation in the control of stem cell self-renewal/differentiation. Collaborations with proteomic facilities and stem cell core laboratory at the Hillman Cancer Center will be involved. Candidates with strong background in stem cell biology (human embryonic stem cell culture) are encouraged to send their curriculum vitae and three references to: **Dr. Yong Wan Ph.D., University of Pittsburgh Cancer Institute, Hillman Cancer Center, 5117 Centre Avenue, Room 2.6C, Pittsburgh, PA 15213. E-mail: yow4@pitt.edu.** Laboratory **website: http://www.cbp.pitt.edu/faculty/yong_wan.**

POSITIONS OPEN

The U.S. Geological Survey's Patuxent Wildlife Research Center in Laurel, Maryland **(website: http://www.pwrc.usgs.gov/),** seeks a **RESEARCH BIOLOGIST** to concentrate on threatened and endangered species, and work with Patuxent's captive flock of breeding whooping cranes. Experience working with cranes is not required. Research results will contribute to advancements in the conservation of threatened and endangered species through captive breeding, restoration techniques, management of restored populations, or other aspects of the ecology and biology of imperiled species. Specific research expertise for this work may come from a range of organismal and ecological disciplines; one can qualify through the Office of Personnel Management standards as a **PHYSIOLOGIST, ZOOLOGIST, or ECOLOGIST.** Apply online before 21 December 2006, at **website: http://www.usgs.gov/ohr/oars/.** Details on the position and application are provided at the website.

VISITING ASSISTANT PROFESSOR
Washington College
Academic Year 2007-2008

Washington College is seeking a full-time **VISITING ASSISTANT PROFESSOR** (nontenure-track/sabbatical replacement) in microbiology for academic year 2007-2008. Teaching responsibilities include introductory biology, microbiology and another upper-level course (immunology preferred) and supervision of undergraduate research. See **website: http://hr.washcoll.edu/** for full application details. *Washington College is an Equal Opportunity Employer. Women and minorities are strongly encouraged to apply.*

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